Search history


```
=> d his full

     (FILE 'HOME' ENTERED AT 09:06:35 ON 06 MAR 2006)

     FILE 'REGISTRY' ENTERED AT 09:06:42 ON 06 MAR 2006
               E RIFALAZIL/CN
L1           1 SEA ABB=ON  PLU=ON  RIFALAZIL/CN
               D SCA

     FILE 'STNGUIDE' ENTERED AT 09:08:41 ON 06 MAR 2006

     FILE 'CAPLUS' ENTERED AT 09:09:18 ON 06 MAR 2006

     FILE 'HCAPLUS' ENTERED AT 09:09:25 ON 06 MAR 2006
               E US2003-668792/APPS
L2           3 SEA ABB=ON  PLU=ON  US2003-668792/AP
               D SCA

     FILE 'REGISTRY' ENTERED AT 09:11:27 ON 06 MAR 2006
L3             STR 129791-92-0
L4           0 SEA FAM SAM L3

     FILE 'REGISTRY' ENTERED AT 09:11:47 ON 06 MAR 2006
L5           1 SEA FAM FUL L3
               SAVE TEMP SPI792FAM/A L5
L6           1 SEA ABB=ON  PLU=ON  L5 AND L1

     FILE 'HCAPLUS' ENTERED AT 09:13:31 ON 06 MAR 2006
L7         110 SEA ABB=ON  PLU=ON  L5

     FILE 'STNGUIDE' ENTERED AT 09:13:46 ON 06 MAR 2006

     FILE 'HCAPLUS' ENTERED AT 09:13:56 ON 06 MAR 2006
               D SCA L2

     FILE 'STNGUIDE' ENTERED AT 09:14:11 ON 06 MAR 2006

     FILE 'HCAPLUS' ENTERED AT 09:46:29 ON 06 MAR 2006
L8          43 SEA ABB=ON  PLU=ON  CABANA B?/AU
L9         222 SEA ABB=ON  PLU=ON  MICHAELIS A?/AU
L10          3 SEA ABB=ON  PLU=ON  MAGNANT G?/AU
L11         29 SEA ABB=ON  PLU=ON  SAYADA C?/AU
L12          2 SEA ABB=ON  PLU=ON  (CABANA B?/AU AND (MICHAELIS A?/AU OR
               MAGNANT G?/AU OR  SAYADA C?/AU))
L13          4 SEA ABB=ON  PLU=ON  (MICHAELIS A?/AU AND  ( MAGNANT G?/AU OR
               SAYADA C?/AU))
L14          0 SEA ABB=ON  PLU=ON  MAGNANT G?/AU AND  SAYADA C?/AU
L15          5 SEA ABB=ON  PLU=ON  (L12 OR L13 OR L14)

     FILE 'STNGUIDE' ENTERED AT 09:47:15 ON 06 MAR 2006

     FILE 'HCAPLUS' ENTERED AT 09:47:48 ON 06 MAR 2006
L16         10 SEA ABB=ON  PLU=ON  L7 AND ((L8 OR L9 OR L10 OR L11))

     FILE 'STNGUIDE' ENTERED AT 09:48:33 ON 06 MAR 2006

     FILE 'REGISTRY' ENTERED AT 09:50:07 ON 06 MAR 2006
               D STAT QUE L5
               D IDE L5 1
```

```
     FILE 'MEDLINE' ENTERED AT 09:52:22 ON 06 MAR 2006
L17           92 SEA ABB=ON  PLU=ON  L5

     FILE 'STNGUIDE' ENTERED AT 09:53:52 ON 06 MAR 2006

     FILE 'MEDLINE' ENTERED AT 09:54:58 ON 06 MAR 2006
L18          122 SEA ABB=ON  PLU=ON  RIFALAZIL OR ABI 1648 OR ABI1648 OR
                 KRM1648 OR KRM 1648
L19           36 SEA ABB=ON  PLU=ON  CABANA B?/AU
L20           44 SEA ABB=ON  PLU=ON  MICHAELIS A?/AU
L21            1 SEA ABB=ON  PLU=ON  MAGNANT G?/AU
L22           30 SEA ABB=ON  PLU=ON  SAYADA C?/AU
L23            0 SEA ABB=ON  PLU=ON  (CABANA B?/AU AND (MICHAELIS A?/AU OR
                 MAGNANT G?/AU OR  SAYADA C?/AU))
L24            0 SEA ABB=ON  PLU=ON  (MICHAELIS A?/AU AND  ( MAGNANT G?/AU OR
                 SAYADA C?/AU))
L25            0 SEA ABB=ON  PLU=ON  MAGNANT G?/AU AND  SAYADA C?/AU
L26            1 SEA ABB=ON  PLU=ON  (L19 OR L20 OR L21 OR L22) AND (L17 OR
                 L18)
                 D TRIAL 1

     FILE 'EMBASE' ENTERED AT 09:57:39 ON 06 MAR 2006
L27           19 SEA ABB=ON  PLU=ON  CABANA B?/AU
L28           39 SEA ABB=ON  PLU=ON  MICHAELIS A?/AU
L29            0 SEA ABB=ON  PLU=ON  MAGNANT G?/AU
L30           32 SEA ABB=ON  PLU=ON  SAYADA C?/AU
L31            0 SEA ABB=ON  PLU=ON  (CABANA B?/AU AND (MICHAELIS A?/AU OR
                 MAGNANT G?/AU OR  SAYADA C?/AU))
L32            0 SEA ABB=ON  PLU=ON  (MICHAELIS A?/AU AND  ( MAGNANT G?/AU OR
                 SAYADA C?/AU))
L33            0 SEA ABB=ON  PLU=ON  MAGNANT G?/AU AND  SAYADA C?/AU
L34          191 SEA ABB=ON  PLU=ON  L5
L35          193 SEA ABB=ON  PLU=ON  RIFALAZIL OR ABI 1648 OR ABI1648 OR
                 KRM1648 OR KRM 1648
L36            1 SEA ABB=ON  PLU=ON  (L27 OR L28 OR L29 OR L30) AND (L34 OR
                 L35)
                 D TRIAL 1

     FILE 'BIOSIS' ENTERED AT 09:59:56 ON 06 MAR 2006
L37          126 SEA ABB=ON  PLU=ON  L5
L38          138 SEA ABB=ON  PLU=ON  RIFALAZIL OR ABI 1648 OR ABI1648 OR
                 KRM1648 OR KRM 1648
L39           32 SEA ABB=ON  PLU=ON  CABANA B?/AU
L40           67 SEA ABB=ON  PLU=ON  MICHAELIS A?/AU
L41            0 SEA ABB=ON  PLU=ON  MAGNANT G?/AU
L42           89 SEA ABB=ON  PLU=ON  SAYADA C?/AU
L43            0 SEA ABB=ON  PLU=ON  (CABANA B?/AU AND (MICHAELIS A?/AU OR
                 MAGNANT G?/AU OR  SAYADA C?/AU))
L44            0 SEA ABB=ON  PLU=ON  (MICHAELIS A?/AU AND  ( MAGNANT G?/AU OR
                 SAYADA C?/AU))
L45            0 SEA ABB=ON  PLU=ON  MAGNANT G?/AU AND  SAYADA C?/AU
L46            2 SEA ABB=ON  PLU=ON  (L37 OR L38) AND (L39 OR L40 OR L41 OR
                 L42)
                 D SCA

     FILE 'STNGUIDE' ENTERED AT 10:01:50 ON 06 MAR 2006

     FILE 'HCAPLUS' ENTERED AT 10:35:53 ON 06 MAR 2006
L47           83 SEA ABB=ON  PLU=ON  L5 (L) (THU OR BAC OR PAC OR PKT OR
                 DMA)/RL
```

```
L48       44638 SEA ABB=ON  PLU=ON  ATHEROSCLER?/OBI OR ATHEROGEN?/OBI OR
                ATHEROM?/OBI  OR ARTERIOSCLER?/OBI
L49       35764 SEA ABB=ON  PLU=ON  CORONAR?/OBI
L50             QUE ABB=ON  PLU=ON  MYOCARD?/OBI OR CARDIO?/OBI
L51             QUE ABB=ON  PLU=ON  ANGINA/OBI OR ANGOR PECTORIS/OBI OR
                STENOCARD?/OBI
L52             QUE ABB=ON  PLU=ON  APOPLEX?/OBI OR STROKE/OBI OR CEREBROVASC?/
                OBI
L53             QUE ABB=ON  PLU=ON  (CEREBR?/OBI OR BRAIN?/OBI) (2A) (ISCHEM?/O
                BI OR ISCHAEM?/OBI)
L54             QUE ABB=ON  PLU=ON  INTERMITT?/OBI (2A) CLAUDICAT?/OBI
L55             QUE ABB=ON  PLU=ON  GANGREN?/OBI
L56             QUE ABB=ON  PLU=ON  MESENTER?/OBI
L57             QUE ABB=ON  PLU=ON  ARTERITIS/OBI OR AORTIT?/OBI OR HORTON?/OBI

L58             QUE ABB=ON  PLU=ON  RENAL ARTER?/OBI (2A) (OBSTRUCT?/OBI OR
                STENO?/OBI)
L59           7 SEA ABB=ON  PLU=ON  L47 AND (L48 OR L49 OR L50 OR L51 OR L52
                OR L53 OR L54 OR L55 OR L56 OR L57 OR L58)
L60           8 SEA ABB=ON  PLU=ON  L5 AND (L48 OR L49 OR L50 OR L51 OR L52 OR
                L53 OR L54 OR L55 OR L56 OR L57 OR L58)
L61             QUE ABB=ON  PLU=ON  (?MYOCARD? OR ?CARDIO?)/BI
L62             QUE ABB=ON  PLU=ON  (?ATHEROSCLER? OR ?ATHEROGEN? OR ?ATHEROM?
                 OR ?ARTERIOSCLER?)/BI
L63             QUE ABB=ON  PLU=ON  ?CORON?/BI
L64             QUE ABB=ON  PLU=ON  (?ANGINA OR ANGOR PECTORIS OR ?STENOCARD?)/
                BI
L65             QUE ABB=ON  PLU=ON  (?APOPLEX? OR ?STROKE? OR ?CEREBROVASC?)/BI

L66       20307 SEA ABB=ON  PLU=ON  ((CEREBR? OR BRAIN?) (2A) (ISCHEM? OR
                ISCHAEM?))/BI
L67         549 SEA ABB=ON  PLU=ON  (INTERMITT? (2A) CLAUDICAT?)/BI
L68             QUE ABB=ON  PLU=ON  ?GANGREN?/BI
L69             QUE ABB=ON  PLU=ON  ?MESENTER?/BI
L*** DEL        QUE ?ARTERITIS OR ?AORTIT? OR HORTON?
L70             QUE ABB=ON  PLU=ON  (?ARTERITIS OR ?AORTIT? OR HORTON?)/BI
L71             QUE ABB=ON  PLU=ON  (?RENAL ARTER? (2A) (OBSTRUCT? OR STENO?))/
                BI
L72           8 SEA ABB=ON  PLU=ON  (L61 OR L62 OR L63 OR L64 OR L65 OR L66 OR
                L67 OR L68 OR L69 OR L70 OR L71) AND (L47 OR L5)
L73             QUE ABB=ON  PLU=ON  ?INFLAMM?/BI
L74             QUE ABB=ON  PLU=ON  (?ANTIBACT? OR ?ANTI BACT?)/BI
L75             QUE ABB=ON  PLU=ON  PLATELET/BI
L*** DEL        QUE ?COAGUL?
L76             QUE ABB=ON  PLU=ON  ?COAGUL?/BI
                E ANTIPYRETIC/CT
                E E3+ALL
                E ANTIPYRETIC/CT
                E E4+ALL
L77             QUE ABB=ON  PLU=ON  ?ANTIPYRET?/BI
                E LIPID-LOWER/CT
                E E5+ALL
                E E2+ALL
L78             QUE ABB=ON  PLU=ON  HYPOLEMIC AGENTS+NT/CT
L79           7 SEA ABB=ON  PLU=ON  (L59 OR L60 OR L72) AND (L73 OR L74 OR L75
                OR L76 OR L77 OR L78)
L80       15159 SEA ABB=ON  PLU=ON  HYPOLIPEMIC AGENTS+NT/CT
L81           4 SEA ABB=ON  PLU=ON  (L59 OR L60 OR L72) AND L80
L82           6 SEA ABB=ON  PLU=ON  (L8 OR L9 OR L10 OR L11) AND (L59 OR L60
                OR L72 OR L79 OR L81)
```

```
     FILE 'MEDLINE' ENTERED AT 10:56:13 ON 06 MAR 2006
L83         81311 SEA ABB=ON  PLU=ON  ARTERIOSCLEROSIS+NT/CT
L84        266695 SEA ABB=ON  PLU=ON  ?CORONAR?
L85        106755 SEA ABB=ON  PLU=ON  MYOCARDIAL INFARCTION+NT/CT
L86         32890 SEA ABB=ON  PLU=ON  ANGINA PECTORIS+NT/CT
L87         35194 SEA ABB=ON  PLU=ON  CEREBROVASCULAR ACCIDENT+NT/CT
L88         36889 SEA ABB=ON  PLU=ON  BRAIN ISCHEMIA+NT/CT
L89          6289 SEA ABB=ON  PLU=ON  INTERMITT? (2A) CLAUDICAT?
L90          6320 SEA ABB=ON  PLU=ON  GANGRENE/CT
L91         40700 SEA ABB=ON  PLU=ON  MESENTER?
L92         20102 SEA ABB=ON  PLU=ON  ?ARTERIT? OR ?AORTIT? OR HORTON?
L93          7970 SEA ABB=ON  PLU=ON  RENAL ARTERY OBSTRUCTION/CT
L94             0 SEA ABB=ON  PLU=ON  (L17 OR L18) AND (L83 OR L84 OR L85 OR L86
                  OR L87 OR L88 OR L89 OR L90 OR L91 OR L92 OR L93)
L95           122 SEA ABB=ON  PLU=ON  (L17 OR L18)
                  D TRIAL 1-5
                  D TRIAL 6-20
                  D TRIAL 21-35
L96        671932 SEA ABB=ON  PLU=ON  ?ARTER?
L97               QUE ABB=ON  PLU=ON  ?HEART? OR ?CARDIO? OR ?CEREBR? OR
                  ?VASCUL? OR ?NECROS?
L98             3 SEA ABB=ON  PLU=ON  L97 AND (L17 OR L18)
                  D TRIAL 1-3
                  D TRIAL L26

     FILE 'EMBASE' ENTERED AT 11:05:31 ON 06 MAR 2006

     FILE 'MEDLINE' ENTERED AT 11:05:39 ON 06 MAR 2006
L99             0 SEA ABB=ON  PLU=ON  L26 AND (L94 OR L98)

     FILE 'EMBASE' ENTERED AT 11:06:16 ON 06 MAR 2006
L100          198 SEA ABB=ON  PLU=ON  (L34 OR L35)
                  E ARTERIOSCLEROSIS+ALL/CT
L101        76713 SEA ABB=ON  PLU=ON  ARTERIOSCLEROSIS+NT/CT
L102       204748 SEA ABB=ON  PLU=ON  ?CORONAR?
                  E MYOCARDIAL INFARCTION+ALL/CT
                  E E2+ALL
L103            0 SEA ABB=ON  PLU=ON  MYOCARDIAL INFARCTION+NT/CT
L104     1084849 SEA ABB=ON  PLU=ON  ?HEART? OR ?CARDIO? OR ?CARDIAC? OR
                  ?CORONAR? OR ?INFARCT?
L105       101601 SEA ABB=ON  PLU=ON  HEART INFARCTION+NT/CT
                  E ANGINA PECTORIS+ALL/CT
L106        35812 SEA ABB=ON  PLU=ON  ANGINA PECTORIS+NT/CT
L107        43618 SEA ABB=ON  PLU=ON  ANGINA?
                  E CEREBROVASCULAR ACCIDENT+ALL/CT
L108       157618 SEA ABB=ON  PLU=ON  CEREBROVASCULAR ACCIDENT+ALL/CT
                  E BRAIN ISCHEMIA+ALL/CT
L109        35653 SEA ABB=ON  PLU=ON  BRAIN ISCHEMIA+NT/CT
                  E INTERMITTANT CLAUDICATION+ALL/CT
                  E E26+ALL
L*** DEL        0 S INTERMITTANT CLAUDICATION+NT/CT
L110         3928 SEA ABB=ON  PLU=ON  INTERMITTENT CLAUDICATION+NT/CT
L111       180358 SEA ABB=ON  PLU=ON  GANGREN? OR NECROS?
                  E NECROSIS+ALL/CT
                  E GANGRENE/CT
L112         8956 SEA ABB=ON  PLU=ON  GANGREN?
                  E MESENTER/CT
                  E E7+ALL
L113        31453 SEA ABB=ON  PLU=ON  MESENTER?
```

```
L114      13311 SEA ABB=ON  PLU=ON  ?ARTERIT? OR ?AORTIT? OR HORTON?
                E RENAL ARTERY OBSTRUCTION+ALL/CT
                E E2+ALL
L115       5423 SEA ABB=ON  PLU=ON  KIDNEY ARTERY STENOSIS/CT
L116     583300 SEA ABB=ON  PLU=ON  ?ARTER?
L117         16 SEA ABB=ON  PLU=ON  L100 AND ((L101 OR L102 OR L103 OR L104 OR
                L105 OR L106 OR L107 OR L108 OR L109 OR L110 OR L111 OR L112
                OR L113 OR L114 OR L115))
                D TRIAL 1-16
L118          0 SEA ABB=ON  PLU=ON  L36 AND L117
L119      89144 SEA ABB=ON  PLU=ON  ?ATHERO?
L120          2 SEA ABB=ON  PLU=ON  L100 AND L119
                D TRIAL 1-2

     FILE 'BIOSIS' ENTERED AT 11:19:40 ON 06 MAR 2006
L121            QUE ABB=ON  PLU=ON  ?ATHERO? OR ?ARTER? OR ?CORONAR? OR
                ?CARDIO? OR ?CARDIAC? OR ?ISCHEM? OR STROKE? OR ?ISCHAEM? OR
                ?BRAIN? OR ?CEREBR?
L*** DEL     126 S L5
L122         138 SEA ABB=ON  PLU=ON  (L37 OR L38)
L123           2 SEA ABB=ON  PLU=ON  L122 AND L121
L124             QUE ABB=ON  PLU=ON  ?HEART? OR ?CARDIAL OR ANGINA? OR ?CLAUDIC?
                 OR ?GANGREN? OR ?NECROS? OR ?MESENT?
L125           5 SEA ABB=ON  PLU=ON  L122 AND L124
L126             QUE ABB=ON  PLU=ON  ?ARTERIT? OR ?AORTIT? OR HORTON?
L127           0 SEA ABB=ON  PLU=ON  L122 AND L126
L128           0 SEA ABB=ON  PLU=ON  L46 AND (L123 OR L125 OR L127)

     FILE 'REGISTRY' ENTERED AT 11:25:07 ON 06 MAR 2006

     FILE 'STNGUIDE' ENTERED AT 11:25:18 ON 06 MAR 2006

     FILE 'REGISTRY' ENTERED AT 11:25:55 ON 06 MAR 2006
                D IDE L5

     INDEX '1MOBILITY, 2MOBILITY, ABI-INFORM, ADISCTI, AEROSPACE, AGRICOLA,
     ALUMINIUM, ANABSTR, ANTE, APOLLIT, AQUALINE, AQUASCI, AQUIRE, BABS,
     BIBLIODATA, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, BLLDB,
     CABA, CAOLD, CAPLUS, CASREACT, CBNB, CEABA-VTB, ...' ENTERED AT 11:27:26
     ON 06 MAR 2006
                SEA RIFALAZIL AND (ARTER? OR ATHERO? OR ?ISCHEM?)
               ---------
               0*  FILE 1MOBILITY
               0*  FILE 2MOBILITY
               0*  FILE ADISCTI
               0*  FILE AGRICOLA
               0*  FILE ALUMINIUM
               0*  FILE APOLLIT
               0*  FILE AQUASCI
               0*  FILE AQUIRE
               0*  FILE BABS
               0*  FILE BIBLIODATA
               2   FILE BIOSIS
               0*  FILE BIOTECHABS
               0*  FILE BIOTECHDS
               0*  FILE BLLDB
               7*  FILE CAPLUS
               4   FILE CBNB
               0*  FILE CEABA-VTB
               0*  FILE CHEMINFORMRX
```

```
                0*  FILE CHEMSAFE
                0*  FILE COMPUSCIENCE
                0*  FILE CONFSCI
                0*  FILE CORROSION
                0*  FILE CROPB
                0*  FILE CROPU
                0*  FILE CSNB
                0*  FILE DDFB
                0*  FILE DDFU
                0*  FILE DETHERM
                0*  FILE DGENE
                1*  FILE DPCI
                0*  FILE DRUGB
                0*  FILE DRUGU
                0*  FILE EMA
                0*  FILE EMBAL
                3   FILE EMBASE
                0*  FILE ENCOMPLIT
                0*  FILE ENCOMPPAT
                0*  FILE ESBIOBASE
                0*  FILE FOMAD
                0*  FILE FORIS
                0*  FILE GEOREF
                0*  FILE HEALSAFE
                0*  FILE ICONDA
                0*  FILE IFICLS
                5   FILE IFIPAT
                2*  FILE IMSDRUGNEWS
                0*  FILE INFODATA
                0*  FILE INIS
                0*  FILE INSPHYS
                0*  FILE INVESTEXT
                0*  FILE IPA
                0*  FILE ITRD
                0*  FILE JICST-EPLUS
                0*  FILE LIFESCI
                0*  FILE MATBUS
                1   FILE MEDLINE
                0*  FILE NIOSHTIC
                8*  FILE NLDB
                0*  FILE NUTRACEUT
                0*  FILE OCEAN
                0*  FILE PAPERCHEM2

     FILE 'HCAPLUS' ENTERED AT 11:32:25 ON 06 MAR 2006
L129            7 SEA ABB=ON  PLU=ON  RIFALAZIL/OBI AND (ARTER?/OBI OR ATHERO?/OB
                  I OR ?ISCHEM?/OBI)
L130            7 SEA ABB=ON  PLU=ON  (RIFALAZIL AND (ARTER? OR ATHERO? OR
                  ?ISCHEM?))/BI
L131            6 SEA ABB=ON  PLU=ON  L130 AND ((L15 OR L16) OR L82)

     FILE 'STNGUIDE' ENTERED AT 11:33:26 ON 06 MAR 2006

     FILE 'USPATFULL' ENTERED AT 11:36:28 ON 06 MAR 2006
L132           21 SEA ABB=ON  PLU=ON  L5
L133           38 SEA ABB=ON  PLU=ON  RIFALAZIL OR ABI 1648 OR ABI1648 OR
                  KRM1648 OR KRM 1648
L134       303236 SEA ABB=ON  PLU=ON  ?ARTER? OR ?ATHERO?
L135           13 SEA ABB=ON  PLU=ON  (L132 OR L133) AND L134
                  D KWIC
```

```
                D KWIC 1-13
L136            3 SEA ABB=ON  PLU=ON  CABANA B?/AU
L137           55 SEA ABB=ON  PLU=ON  MICHAELIS A?/AU
L138           16 SEA ABB=ON  PLU=ON  MAGNANT G?/AU
L139           10 SEA ABB=ON  PLU=ON  SAYADA C?/AU
L140            3 SEA ABB=ON  PLU=ON  (CABANA B?/AU AND (MICHAELIS A?/AU OR
                  MAGNANT G?/AU OR  SAYADA C?/AU))
L141            5 SEA ABB=ON  PLU=ON  (MICHAELIS A?/AU AND  ( MAGNANT G?/AU OR
                  SAYADA C?/AU))
L142            2 SEA ABB=ON  PLU=ON  MAGNANT G?/AU AND  SAYADA C?/AU
L143            7 SEA ABB=ON  PLU=ON  (L140 OR L141 OR L142)
L144           10 SEA ABB=ON  PLU=ON  (L132 OR L133) AND (L136 OR L137 OR L138
                  OR L139)
L145           10 SEA ABB=ON  PLU=ON  (L143 OR L144) AND L135
L146              QUE ABB=ON  PLU=ON  ?HEART? OR ?CARDIO? OR ?CARDIA? OR
                  ?ANGINA? OR STROKE? OR ?CEREBR? OR ?BRAIN? OR ?CLAUDIC? OR
                  GANGREN? OR ?ISCHEM? OR ?ISCHAEM?
L147           28 SEA ABB=ON  PLU=ON  (L132 OR L133) AND L146
L148            9 SEA ABB=ON  PLU=ON  L147 AND (L136 OR L137 OR L138 OR L139)
L149           19 SEA ABB=ON  PLU=ON  L147 NOT L148
                D KWIC 1
L150           26 SEA ABB=ON  PLU=ON  (L132 OR L133) (L) L146
L151            7 SEA ABB=ON  PLU=ON  (L132 OR L133) (P) L146
L152            4 SEA ABB=ON  PLU=ON  L151 NOT L148
                D KWIC 1-4
L153           10 SEA ABB=ON  PLU=ON  (L136 OR L137 OR L138 OR L139) AND L135
L154            3 SEA ABB=ON  PLU=ON  (L136 OR L137 OR L138 OR L139) AND L151

     FILE 'STNGUIDE' ENTERED AT 11:48:41 ON 06 MAR 2006

     FILE 'HCAPLUS' ENTERED AT 11:53:55 ON 06 MAR 2006
                D QUE NOS L15
                D QUE NOS L16
                D QUE NOS L82
                D QUE NOS L131
L155           11 SEA ABB=ON  PLU=ON  L15 OR L16 OR L82 OR L131

     FILE 'MEDLINE' ENTERED AT 11:54:01 ON 06 MAR 2006
                D QUE NOS L23
                D QUE NOS L24
                D QUE NOS L25
                D QUE NOS L26
                D QUE NOS L99
L156            1 SEA ABB=ON  PLU=ON  (L23 OR L24 OR L25 OR L26) OR L99

     FILE 'EMBASE' ENTERED AT 11:54:05 ON 06 MAR 2006
                D QUE NOS L31
                D QUE NOS L32
                D QUE NOS L33
                D QUE NOS L36
                D QUE NOS L118
L157            1 SEA ABB=ON  PLU=ON  (L31 OR L32 OR L33) OR L36 OR L118

     FILE 'BIOSIS' ENTERED AT 11:54:10 ON 06 MAR 2006
                D QUE NOS L43
                D QUE NOS L44
                D QUE NOS L45
                D QUE NOS L46
                D QUE NOS L128
L158            2 SEA ABB=ON  PLU=ON  (L43 OR L44 OR L45 OR L46) OR L128
```

```
     FILE 'USPATFULL' ENTERED AT 11:54:16 ON 06 MAR 2006
                D QUE NOS L143
                D QUE NOS L144
                D QUE NOS L148
                D QUE NOS L153
                D QUE NOS L154
L159          12 SEA ABB=ON  PLU=ON  (L143 OR L144) OR L148 OR (L153 OR L154)

     FILE 'STNGUIDE' ENTERED AT 11:54:28 ON 06 MAR 2006

     FILE 'HCAPLUS, MEDLINE, EMBASE, BIOSIS, USPATFULL' ENTERED AT 11:55:27 ON
     06 MAR 2006
L160          21 DUP REM L155 L156 L157 L158 L159 (6 DUPLICATES REMOVED)
                     ANSWERS '1-11' FROM FILE HCAPLUS
                     ANSWER '12' FROM FILE BIOSIS
                     ANSWERS '13-21' FROM FILE USPATFULL
                D IBIB ABS HITIND HITSTR L160 1-11
                D IALL L160 12
                D IBIB ABS KWIC HITSTR L160 13-21

     FILE 'STNGUIDE' ENTERED AT 11:57:13 ON 06 MAR 2006

     FILE 'HCAPLUS' ENTERED AT 12:00:49 ON 06 MAR 2006
                D QUE NOS L59
                D QUE NOS L60
                D QUE NOS L72
                D QUE NOS L79
                D QUE NOS L81
                D QUE NOS L130
L161           2 SEA ABB=ON  PLU=ON  ((L59 OR L60) OR L72 OR L79 OR L81 OR
                  L130) NOT L155

     FILE 'MEDLINE' ENTERED AT 12:00:54 ON 06 MAR 2006
                D QUE NOS L94
                D QUE NOS L98
L162           3 SEA ABB=ON  PLU=ON  (L94 OR L98) NOT L156

     FILE 'EMBASE' ENTERED AT 12:00:57 ON 06 MAR 2006
                D QUE NOS L117
                D QUE NOS L120
L163          16 SEA ABB=ON  PLU=ON  (L117 OR L120) NOT L157

     FILE 'BIOSIS' ENTERED AT 12:01:00 ON 06 MAR 2006
                D QUE NOS L123
                D QUE NOS L125
                D QUE NOS L127
L164           7 SEA ABB=ON  PLU=ON  (L123 OR L125 OR L127) NOT L158

     FILE 'USPATFULL' ENTERED AT 12:01:04 ON 06 MAR 2006
                D QUE NOS L135
                D QUE NOS L151
                D QUE NOS L147
L165          20 SEA ABB=ON  PLU=ON  (L135 OR L151 OR L147) NOT L159

     FILE 'STNGUIDE' ENTERED AT 12:01:22 ON 06 MAR 2006

     FILE 'HCAPLUS, MEDLINE, EMBASE, BIOSIS, USPATFULL' ENTERED AT 12:02:20 ON
     06 MAR 2006
L166          40 DUP REM L161 L162 L163 L164 L165 (8 DUPLICATES REMOVED)
```

```
     ANSWERS '1-2' FROM FILE HCAPLUS
     ANSWERS '3-5' FROM FILE MEDLINE
     ANSWERS '6-17' FROM FILE EMBASE
     ANSWERS '18-20' FROM FILE BIOSIS
     ANSWERS '21-40' FROM FILE USPATFULL
D IBIB ABS HITIND HITSTR L166 1-2
D IALL L166 3-20
D IBIB ABS KWIC HITSTR L166 21-40

FILE HOME

FILE REGISTRY
Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:    5 MAR 2006  HIGHEST RN 875875-45-9
DICTIONARY FILE UPDATES:   5 MAR 2006  HIGHEST RN 875875-45-9

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

*************************************************************
*                                                           *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005.  A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*                                                           *
*************************************************************

Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

FILE STNGUIDE
FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Mar  3, 2006 (20060303/UP).

FILE CAPLUS

Copyright of the articles to which records in this database refer is
held by the publishers listed in the PUBLISHER (PB) field (available
for records published or updated in Chemical Abstracts after December
26, 1996), unless otherwise indicated in the original publications.
The CA Lexicon is the copyrighted intellectual property of the
American Chemical Society and is provided to assist you in searching
databases on STN.  Any dissemination, distribution, copying, or storing
of this information, without the prior written consent of CAS, is
strictly prohibited.
```

FILE COVERS 1907 - 6 Mar 2006 VOL 144 ISS 11
FILE LAST UPDATED: 5 Mar 2006 (20060305/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

http://www.cas.org/infopolicy.html

FILE HCAPLUS

FILE COVERS 1907 - 6 Mar 2006 VOL 144 ISS 11
FILE LAST UPDATED: 5 Mar 2006 (20060305/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

FILE MEDLINE
FILE LAST UPDATED: 4 MAR 2006 (20060304/UP). FILE COVERS 1950 TO DATE.

On December 11, 2005, the 2006 MeSH terms were loaded.

The MEDLINE reload for 2006 is now (26 Feb.) available. For details
on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

OLDMEDLINE is covered back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
MeSH 2006 vocabulary.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

FILE EMBASE
FILE COVERS 1974 TO 3 Mar 2006 (20060303/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

FILE BIOSIS

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

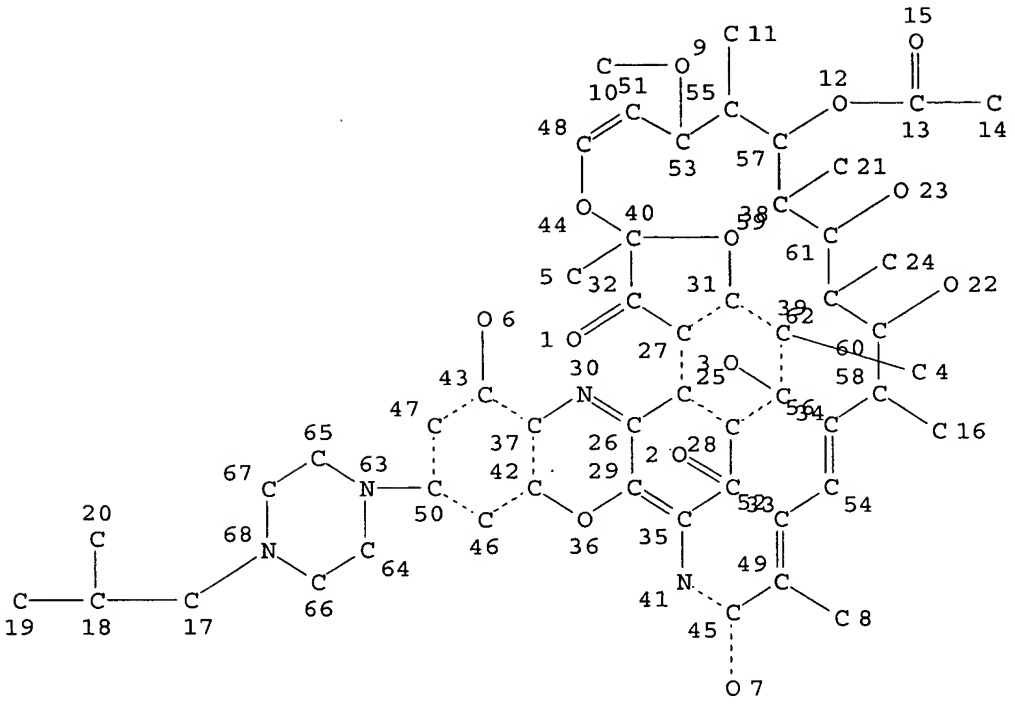
RECORDS LAST ADDED: 1 March 2006 (20060301/ED)

FILE STNINDEX

FILE USPATFULL
FILE COVERS 1971 TO PATENT PUBLICATION DATE: 2 Mar 2006 (20060302/PD)
FILE LAST UPDATED: 2 Mar 2006 (20060302/ED)
HIGHEST GRANTED PATENT NUMBER: US7007305
HIGHEST APPLICATION PUBLICATION NUMBER: US2006048257
CA INDEXING IS CURRENT THROUGH 28 Feb 2006 (20060228/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 2 Mar 2006 (20060302/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2005

=>

```
=> file registry
FILE 'REGISTRY' ENTERED AT 09:50:07 ON 06 MAR 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:    5 MAR 2006  HIGHEST RN 875875-45-9
DICTIONARY FILE UPDATES:   5 MAR 2006  HIGHEST RN 875875-45-9

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

*********************************************************************
*                                                                   *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005.  A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*                                                                   *
*********************************************************************

Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> d stat que L5
L3              STR
```



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 68

STEREO ATTRIBUTES: NONE
L5 1 SEA FILE=REGISTRY FAM FUL L3 FAMILY SEARCH

100.0% PROCESSED 129 ITERATIONS 1 ANSWERS
SEARCH TIME: 00.00.01

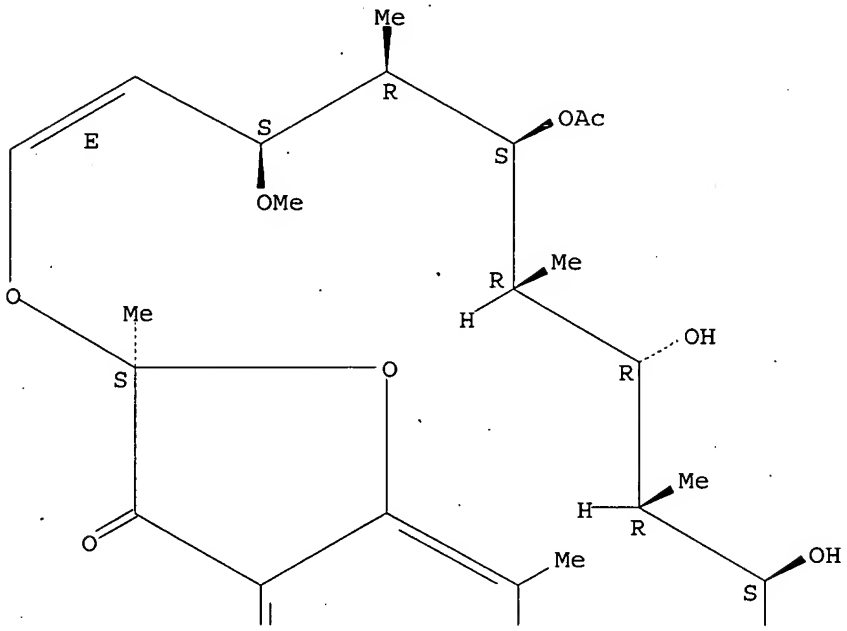
=> d ide L5 1

L5 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2006 ACS on STN
RN 129791-92-0 REGISTRY
ED Entered STN: 12 Oct 1990
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2,7-(Epoxypentadeca[1,11,13]trienimino)-6H-benzofuro[4,5-a]phenoxazine, rifamycin VIII deriv.
OTHER NAMES:
CN ABI 1648
CN KRM 1648
CN Rifalazil
FS STEREOSEARCH
DR 188910-97-6

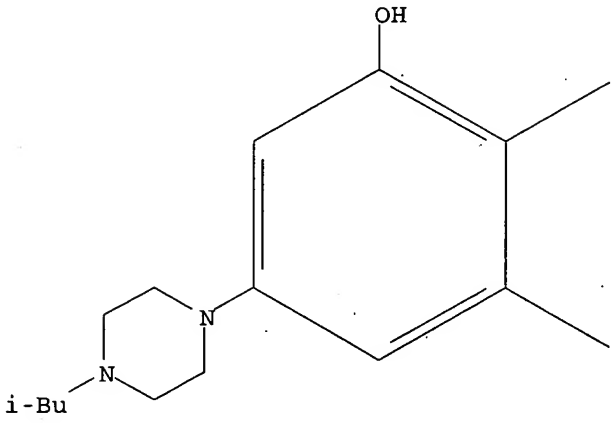
MF C51 H64 N4 O13
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CA, CAPLUS, CBNB, CIN, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, MEDLINE, MRCK*, PHAR, PROMT, PROUSDDR, SCISEARCH, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

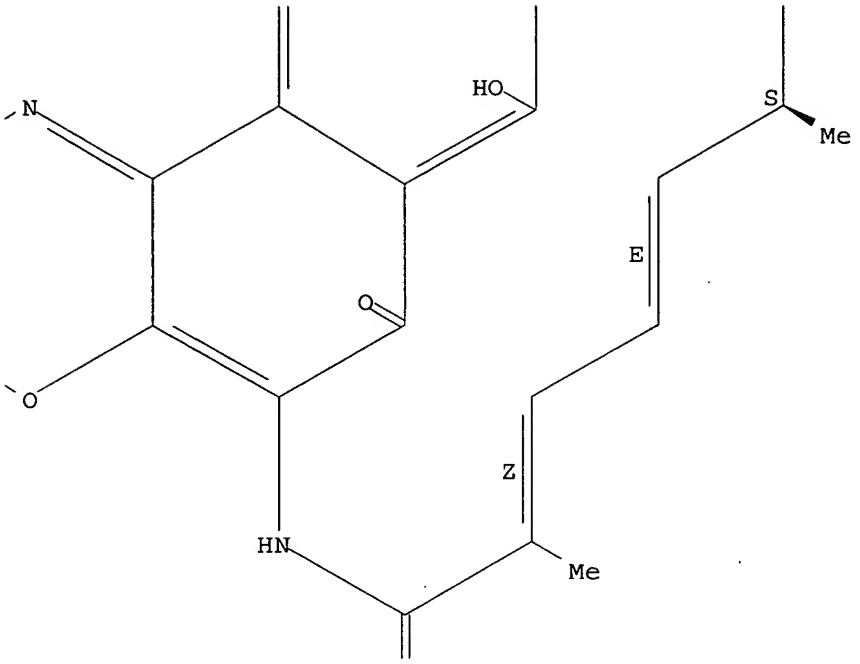
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

O

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

110 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
110 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> => => file hcaplus
FILE 'HCAPLUS' ENTERED AT 11:53:55 ON 06 MAR 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

AUTHOR SEARCH

FILE COVERS 1907 - 6 Mar 2006 VOL 144 ISS 11

```
FILE LAST UPDATED: 5 Mar 2006  (20060305/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.
'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> d que nos L15

L12           2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (CABANA B?/AU AND (MICHAELIS
                A?/AU OR  MAGNANT G?/AU OR  SAYADA C?/AU))
L13           4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (MICHAELIS A?/AU AND  (
                MAGNANT G?/AU OR  SAYADA C?/AU))
L14           0 SEA FILE=HCAPLUS ABB=ON  PLU=ON  MAGNANT G?/AU AND  SAYADA
                C?/AU
L15           5 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L12 OR L13 OR L14)


=> d que nos L16

L3              STR
L5            1 SEA FILE=REGISTRY FAM FUL L3
L7          110 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5
L8           43 SEA FILE=HCAPLUS ABB=ON  PLU=ON  CABANA B?/AU
L9          222 SEA FILE=HCAPLUS ABB=ON  PLU=ON  MICHAELIS A?/AU
L10           3 SEA FILE=HCAPLUS ABB=ON  PLU=ON  MAGNANT G?/AU
L11          29 SEA FILE=HCAPLUS ABB=ON  PLU=ON  SAYADA C?/AU
L16          10 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7 AND ((L8 OR L9 OR L10 OR
                L11))


=> d que nos L82

L3              STR
L5            1 SEA FILE=REGISTRY FAM FUL L3
L8           43 SEA FILE=HCAPLUS ABB=ON  PLU=ON  CABANA B?/AU
L9          222 SEA FILE=HCAPLUS ABB=ON  PLU=ON  MICHAELIS A?/AU
L10           3 SEA FILE=HCAPLUS ABB=ON  PLU=ON  MAGNANT G?/AU
L11          29 SEA FILE=HCAPLUS ABB=ON  PLU=ON  SAYADA C?/AU
L47          83 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5 (L) (THU OR BAC OR PAC OR
                PKT OR DMA)/RL
L48       44638 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ATHEROSCLER?/OBI OR ATHEROGEN?
                /OBI OR ATHEROM?/OBI  OR ARTERIOSCLER?/OBI
L49       35764 SEA FILE=HCAPLUS ABB=ON  PLU=ON  CORONAR?/OBI
L50             QUE  ABB=ON  PLU=ON  MYOCARD?/OBI OR CARDIO?/OBI
L51             QUE  ABB=ON  PLU=ON  ANGINA/OBI OR ANGOR PECTORIS/OBI OR
                STENOCARD?/OBI
L52             QUE  ABB=ON  PLU=ON  APOPLEX?/OBI OR STROKE/OBI OR CEREBR
                OVASC?/OBI
L53             QUE  ABB=ON  PLU=ON  (CEREBR?/OBI OR BRAIN?/OBI) (2A) (IS
                CHEM?/OBI OR ISCHAEM?/OBI)
L54             QUE  ABB=ON  PLU=ON  INTERMITT?/OBI (2A) CLAUDICAT?/OBI
L55             QUE  ABB=ON  PLU=ON  GANGREN?/OBI
L56             QUE  ABB=ON  PLU=ON  MESENTER?/OBI
L57             QUE  ABB=ON  PLU=ON  ARTERITIS/OBI OR AORTIT?/OBI OR HORT
                ON?/OBI
L58             QUE  ABB=ON  PLU=ON  RENAL ARTER?/OBI (2A) (OBSTRUCT?/OBI
                 OR STENO?/OBI)
L59           7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L47 AND (L48 OR L49 OR L50 OR
```

```
                L51 OR L52 OR L53 OR L54 OR L55 OR L56 OR L57 OR L58)
L60           8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5 AND (L48 OR L49 OR L50 OR
                L51 OR L52 OR L53 OR L54 OR L55 OR L56 OR L57 OR L58)
L61             QUE  ABB=ON  PLU=ON  (?MYOCARD? OR ?CARDIO?)/BI
L62             QUE  ABB=ON  PLU=ON  (?ATHEROSCLER? OR ?ATHEROGEN? OR ?AT
                HEROM?  OR ?ARTERIOSCLER?)/BI
L63             QUE  ABB=ON  PLU=ON  ?CORON?/BI
L64             QUE  ABB=ON  PLU=ON  (?ANGINA OR ANGOR PECTORIS OR ?STENO
                CARD?)/BI
L65             QUE  ABB=ON  PLU=ON  (?APOPLEX? OR ?STROKE? OR ?CEREBROVA
                SC?)/BI
L66       20307 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ((CEREBR? OR BRAIN?) (2A)
                (ISCHEM? OR ISCHAEM?))/BI
L67         549 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (INTERMITT? (2A) CLAUDICAT?)/B
                I
L68             QUE  ABB=ON  PLU=ON  ?GANGREN?/BI
L69             QUE  ABB=ON  PLU=ON  ?MESENTER?/BI
L70             QUE  ABB=ON  PLU=ON  (?ARTERITIS OR ?AORTIT? OR HORTON?)/
                BI
L71             QUE  ABB=ON  PLU=ON  (?RENAL ARTER? (2A) (OBSTRUCT? OR ST
                ENO?))/BI
L72           8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L61 OR L62 OR L63 OR L64 OR
                L65 OR L66 OR L67 OR L68 OR L69 OR L70 OR L71) AND (L47 OR L5)
L73             QUE  ABB=ON  PLU=ON  ?INFLAMM?/BI
L74             QUE  ABB=ON  PLU=ON  (?ANTIBACT? OR ?ANTI BACT?)/BI
L75             QUE  ABB=ON  PLU=ON  PLATELET/BI
L76             QUE  ABB=ON  PLU=ON  ?COAGUL?/BI
L77             QUE  ABB=ON  PLU=ON  ?ANTIPYRET?/BI
L78             QUE  ABB=ON  PLU=ON  HYPOLEMIC AGENTS+NT/CT
L79           7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L59 OR L60 OR L72) AND (L73
                OR L74 OR L75 OR L76 OR L77 OR L78)
L80       15159 SEA FILE=HCAPLUS ABB=ON  PLU=ON  HYPOLIPEMIC AGENTS+NT/CT
L81           4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L59 OR L60 OR L72) AND L80
L82           6 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L8 OR L9 OR L10 OR L11) AND
                (L59 OR L60 OR L72 OR L79 OR L81)


=> d que nos L131

L3              STR
L5            1 SEA FILE=REGISTRY FAM FUL L3
L7          110 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5
L8           43 SEA FILE=HCAPLUS ABB=ON  PLU=ON  CABANA B?/AU
L9          222 SEA FILE=HCAPLUS ABB=ON  PLU=ON  MICHAELIS A?/AU
L10           3 SEA FILE=HCAPLUS ABB=ON  PLU=ON  MAGNANT G?/AU
L11          29 SEA FILE=HCAPLUS ABB=ON  PLU=ON  SAYADA C?/AU
L12           2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (CABANA B?/AU AND (MICHAELIS
                A?/AU OR  MAGNANT G?/AU OR  SAYADA C?/AU))
L13           4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (MICHAELIS A?/AU AND  (
                MAGNANT G?/AU OR  SAYADA C?/AU))
L14           0 SEA FILE=HCAPLUS ABB=ON  PLU=ON  MAGNANT G?/AU AND  SAYADA
                C?/AU
L15           5 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L12 OR L13 OR L14)
L16          10 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7 AND ((L8 OR L9 OR L10 OR
                L11))
L47          83 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5 (L) (THU OR BAC OR PAC OR
                PKT OR DMA)/RL
L48       44638 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ATHEROSCLER?/OBI OR ATHEROGEN?
                /OBI OR ATHEROM?/OBI  OR ARTERIOSCLER?/OBI
L49       35764 SEA FILE=HCAPLUS ABB=ON  PLU=ON  CORONAR?/OBI
```

```
L50             QUE  ABB=ON  PLU=ON  MYOCARD?/OBI OR CARDIO?/OBI
L51             QUE  ABB=ON  PLU=ON  ANGINA/OBI OR ANGOR PECTORIS/OBI OR
                STENOCARD?/OBI
L52             QUE  ABB=ON  PLU=ON  APOPLEX?/OBI OR STROKE/OBI OR CEREBR
                OVASC?/OBI
L53             QUE  ABB=ON  PLU=ON  (CEREBR?/OBI OR BRAIN?/OBI) (2A) (IS
                CHEM?/OBI OR ISCHAEM?/OBI)
L54             QUE  ABB=ON  PLU=ON  INTERMITT?/OBI (2A) CLAUDICAT?/OBI
L55             QUE  ABB=ON  PLU=ON  GANGREN?/OBI
L56             QUE  ABB=ON  PLU=ON  MESENTER?/OBI
L57             QUE  ABB=ON  PLU=ON  ARTERITIS/OBI OR AORTIT?/OBI OR HORT
                ON?/OBI
L58             QUE  ABB=ON  PLU=ON  RENAL ARTER?/OBI (2A) (OBSTRUCT?/OBI
                 OR STENO?/OBI)
L59           7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L47 AND (L48 OR L49 OR L50 OR
                L51 OR L52 OR L53 OR L54 OR L55 OR L56 OR L57 OR L58)
L60           8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5 AND (L48 OR L49 OR L50 OR
                L51 OR L52 OR L53 OR L54 OR L55 OR L56 OR L57 OR L58)
L61             QUE  ABB=ON  PLU=ON  (?MYOCARD? OR ?CARDIO?)/BI
L62             QUE  ABB=ON  PLU=ON  (?ATHEROSCLER? OR ?ATHEROGEN? OR ?AT
                HEROM?  OR ?ARTERIOSCLER?)/BI
L63             QUE  ABB=ON  PLU=ON  ?CORON?/BI
L64             QUE  ABB=ON  PLU=ON  (?ANGINA OR ANGOR PECTORIS OR ?STENO
                CARD?)/BI
L65             QUE  ABB=ON  PLU=ON  (?APOPLEX? OR ?STROKE? OR ?CEREBROVA
                SC?)/BI
L66       20307 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ((CEREBR? OR BRAIN?) (2A)
                (ISCHEM? OR ISCHAEM?))/BI
L67         549 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (INTERMITT? (2A) CLAUDICAT?)/B
                I
L68             QUE  ABB=ON  PLU=ON  ?GANGREN?/BI
L69             QUE  ABB=ON  PLU=ON  ?MESENTER?/BI
L70             QUE  ABB=ON  PLU=ON  (?ARTERITIS OR ?AORTIT? OR HORTON?)/
                BI
L71             QUE  ABB=ON  PLU=ON  (?RENAL ARTER? (2A) (OBSTRUCT? OR ST
                ENO?))/BI
L72           8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L61 OR L62 OR L63 OR L64 OR
                L65 OR L66 OR L67 OR L68 OR L69 OR L70 OR L71) AND (L47 OR L5)
L73             QUE  ABB=ON  PLU=ON  ?INFLAMM?/BI
L74             QUE  ABB=ON  PLU=ON  (?ANTIBACT? OR ?ANTI BACT?)/BI
L75             QUE  ABB=ON  PLU=ON  PLATELET/BI
L76             QUE  ABB=ON  PLU=ON  ?COAGUL?/BI
L77             QUE  ABB=ON  PLU=ON  ?ANTIPYRET?/BI
L78             QUE  ABB=ON  PLU=ON  HYPOLEMIC AGENTS+NT/CT
L79           7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L59 OR L60 OR L72) AND (L73
                OR L74 OR L75 OR L76 OR L77 OR L78)
L80       15159 SEA FILE=HCAPLUS ABB=ON  PLU=ON  HYPOLIPEMIC AGENTS+NT/CT
L81           4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L59 OR L60 OR L72) AND L80
L82           6 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L8 OR L9 OR L10 OR L11) AND
                (L59 OR L60 OR L72 OR L79 OR L81)
L130          7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (RIFALAZIL AND (ARTER? OR
                ATHERO? OR ?ISCHEM?))/BI
L131          6 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L130 AND ((L15 OR L16) OR
                L82)


=> s L15 or L16 or L82 or L131

L155         11 L15 OR L16 OR L82 OR L131
```

```
=> file medline

FILE 'MEDLINE' ENTERED AT 11:54:01 ON 06 MAR 2006

 FILE LAST UPDATED: 4 MAR 2006 (20060304/UP).  FILE COVERS 1950 TO DATE.

 On December 11, 2005, the 2006 MeSH terms were loaded.

 The MEDLINE reload for 2006 is now (26 Feb.) available.  For details
 on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
 See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

 OLDMEDLINE is covered back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2006 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d que nos L23

L23             0 SEA FILE=MEDLINE ABB=ON  PLU=ON  (CABANA B?/AU AND (MICHAELIS
                  A?/AU OR  MAGNANT G?/AU OR  SAYADA C?/AU))


=> d que nos L24

L24             0 SEA FILE=MEDLINE ABB=ON  PLU=ON  (MICHAELIS A?/AU AND  (
                  MAGNANT G?/AU OR  SAYADA C?/AU))


=> d que nos L25

L25             0 SEA FILE=MEDLINE ABB=ON  PLU=ON  MAGNANT G?/AU AND  SAYADA
                  C?/AU


=> d que nos L26

L3                STR
L5              1 SEA FILE=REGISTRY FAM FUL L3
L17            92 SEA FILE=MEDLINE ABB=ON  PLU=ON  L5
L18           122 SEA FILE=MEDLINE ABB=ON  PLU=ON  RIFALAZIL OR ABI 1648 OR
                  ABI1648 OR KRM1648 OR KRM 1648
L19            36 SEA FILE=MEDLINE ABB=ON  PLU=ON  CABANA B?/AU
L20            44 SEA FILE=MEDLINE ABB=ON  PLU=ON  MICHAELIS A?/AU
L21             1 SEA FILE=MEDLINE ABB=ON  PLU=ON  MAGNANT G?/AU
L22            30 SEA FILE=MEDLINE ABB=ON  PLU=ON  SAYADA C?/AU
L26             1 SEA FILE=MEDLINE ABB=ON  PLU=ON  (L19 OR L20 OR L21 OR L22)
                  AND (L17 OR L18)


=> d que nos L99
```

```
L3              STR
L5            1 SEA FILE=REGISTRY FAM FUL L3
L17          92 SEA FILE=MEDLINE ABB=ON  PLU=ON  L5
L18         122 SEA FILE=MEDLINE ABB=ON  PLU=ON  RIFALAZIL OR ABI 1648 OR
                ABI1648 OR KRM1648 OR KRM 1648
L19          36 SEA FILE=MEDLINE ABB=ON  PLU=ON  CABANA B?/AU
L20          44 SEA FILE=MEDLINE ABB=ON  PLU=ON  MICHAELIS A?/AU
L21           1 SEA FILE=MEDLINE ABB=ON  PLU=ON  MAGNANT G?/AU
L22          30 SEA FILE=MEDLINE ABB=ON  PLU=ON  SAYADA C?/AU
L26           1 SEA FILE=MEDLINE ABB=ON  PLU=ON  (L19 OR L20 OR L21 OR L22)
                AND (L17 OR L18)
L83       81311 SEA FILE=MEDLINE ABB=ON  PLU=ON  ARTERIOSCLEROSIS+NT/CT
L84      266695 SEA FILE=MEDLINE ABB=ON  PLU=ON  ?CORONAR?
L85      106755 SEA FILE=MEDLINE ABB=ON  PLU=ON  MYOCARDIAL INFARCTION+NT/CT
L86       32890 SEA FILE=MEDLINE ABB=ON  PLU=ON  ANGINA PECTORIS+NT/CT
L87       35194 SEA FILE=MEDLINE ABB=ON  PLU=ON  CEREBROVASCULAR ACCIDENT+NT/CT

L88       36889 SEA FILE=MEDLINE ABB=ON  PLU=ON  BRAIN ISCHEMIA+NT/CT
L89        6289 SEA FILE=MEDLINE ABB=ON  PLU=ON  INTERMITT? (2A) CLAUDICAT?
L90        6320 SEA FILE=MEDLINE ABB=ON  PLU=ON  GANGRENE/CT
L91       40700 SEA FILE=MEDLINE ABB=ON  PLU=ON  MESENTER?
L92       20102 SEA FILE=MEDLINE ABB=ON  PLU=ON  ?ARTERIT? OR ?AORTIT? OR
                HORTON?
L93        7970 SEA FILE=MEDLINE ABB=ON  PLU=ON  RENAL ARTERY OBSTRUCTION/CT
L94           0 SEA FILE=MEDLINE ABB=ON  PLU=ON  (L17 OR L18) AND (L83 OR L84
                OR L85 OR L86 OR L87 OR L88 OR L89 OR L90 OR L91 OR L92 OR
                L93)
L97             QUE  ABB=ON  PLU=ON  ?HEART? OR ?CARDIO? OR ?CEREBR? OR ?
                VASCUL? OR ?NECROS?
L98           3 SEA FILE=MEDLINE ABB=ON  PLU=ON  L97 AND (L17 OR L18)
L99           0 SEA FILE=MEDLINE ABB=ON  PLU=ON  L26 AND (L94 OR L98)


=> s L23-L26 or L99

L156          1 (L23 OR L24 OR L25 OR L26) OR L99

=> file embase

FILE 'EMBASE' ENTERED AT 11:54:05 ON 06 MAR 2006
Copyright (c) 2006 Elsevier B.V. All rights reserved.

 FILE COVERS 1974 TO 3 Mar 2006 (20060303/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d que nos L31

L31           0 SEA FILE=EMBASE ABB=ON  PLU=ON  (CABANA B?/AU AND (MICHAELIS
                A?/AU OR  MAGNANT G?/AU OR  SAYADA C?/AU))


=> d que nos L32

L32           0 SEA FILE=EMBASE ABB=ON  PLU=ON  (MICHAELIS A?/AU AND  (
                MAGNANT G?/AU OR  SAYADA C?/AU))
```

```
=> d que nos L33

L33             0 SEA FILE=EMBASE ABB=ON  PLU=ON  MAGNANT G?/AU AND  SAYADA
                  C?/AU


=> d que nos L36

L3                STR
L5                1 SEA FILE=REGISTRY FAM FUL L3
L27              19 SEA FILE=EMBASE ABB=ON  PLU=ON  CABANA B?/AU
L28              39 SEA FILE=EMBASE ABB=ON  PLU=ON  MICHAELIS A?/AU
L29               0 SEA FILE=EMBASE ABB=ON  PLU=ON  MAGNANT G?/AU
L30              32 SEA FILE=EMBASE ABB=ON  PLU=ON  SAYADA C?/AU
L34             191 SEA FILE=EMBASE ABB=ON  PLU=ON  L5
L35             193 SEA FILE=EMBASE ABB=ON  PLU=ON  RIFALAZIL OR ABI 1648 OR
                  ABI1648 OR KRM1648 OR KRM 1648
L36               1 SEA FILE=EMBASE ABB=ON  PLU=ON  (L27 OR L28 OR L29 OR L30) AND
                  (L34 OR L35)


=> d que nos L118

L3                STR
L5                1 SEA FILE=REGISTRY FAM FUL L3
L27              19 SEA FILE=EMBASE ABB=ON  PLU=ON  CABANA B?/AU
L28              39 SEA FILE=EMBASE ABB=ON  PLU=ON  MICHAELIS A?/AU
L29               0 SEA FILE=EMBASE ABB=ON  PLU=ON  MAGNANT G?/AU
L30              32 SEA FILE=EMBASE ABB=ON  PLU=ON  SAYADA C?/AU
L34             191 SEA FILE=EMBASE ABB=ON  PLU=ON  L5
L35             193 SEA FILE=EMBASE ABB=ON  PLU=ON  RIFALAZIL OR ABI 1648 OR
                  ABI1648 OR KRM1648 OR KRM 1648
L36               1 SEA FILE=EMBASE ABB=ON  PLU=ON  (L27 OR L28 OR L29 OR L30) AND
                  (L34 OR L35)
L100            198 SEA FILE=EMBASE ABB=ON  PLU=ON  (L34 OR L35)
L101          76713 SEA FILE=EMBASE ABB=ON  PLU=ON  ARTERIOSCLEROSIS+NT/CT
L102         204748 SEA FILE=EMBASE ABB=ON  PLU=ON  ?CORONAR?
L103              0 SEA FILE=EMBASE ABB=ON  PLU=ON  MYOCARDIAL INFARCTION+NT/CT
L104        1084849 SEA FILE=EMBASE ABB=ON  PLU=ON  ?HEART? OR ?CARDIO? OR
                  ?CARDIAC? OR ?CORONAR? OR ?INFARCT?
L105         101601 SEA FILE=EMBASE ABB=ON  PLU=ON  HEART INFARCTION+NT/CT
L106          35812 SEA FILE=EMBASE ABB=ON  PLU=ON  ANGINA PECTORIS+NT/CT
L107          43618 SEA FILE=EMBASE ABB=ON  PLU=ON  ANGINA?
L108         157618 SEA FILE=EMBASE ABB=ON  PLU=ON  CEREBROVASCULAR ACCIDENT+ALL/CT

L109          35653 SEA FILE=EMBASE ABB=ON  PLU=ON  BRAIN ISCHEMIA+NT/CT
L110           3928 SEA FILE=EMBASE ABB=ON  PLU=ON  INTERMITTENT CLAUDICATION+NT/CT

L111         180358 SEA FILE=EMBASE ABB=ON  PLU=ON  GANGREN? OR NECROS?
L112           8956 SEA FILE=EMBASE ABB=ON  PLU=ON  GANGREN?
L113          31453 SEA FILE=EMBASE ABB=ON  PLU=ON  MESENTER?
L114          13311 SEA FILE=EMBASE ABB=ON  PLU=ON  ?ARTERIT? OR ?AORTIT? OR
                  HORTON?
L115           5423 SEA FILE=EMBASE ABB=ON  PLU=ON  KIDNEY ARTERY STENOSIS/CT
L117             16 SEA FILE=EMBASE ABB=ON  PLU=ON  L100 AND ((L101 OR L102 OR
                  L103 OR L104 OR L105 OR L106 OR L107 OR L108 OR L109 OR L110
                  OR L111 OR L112 OR L113 OR L114 OR L115))
L118              0 SEA FILE=EMBASE ABB=ON  PLU=ON  L36 AND L117
```

```
=> s L31-L33 or L36 or L118

L157          1 (L31 OR L32 OR L33) OR L36 OR L118

=> file biosis

FILE 'BIOSIS' ENTERED AT 11:54:10 ON 06 MAR 2006
Copyright (c) 2006 The Thomson Corporation

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 1 March 2006 (20060301/ED)


=> d que nos L43

L43           0 SEA FILE=BIOSIS ABB=ON  PLU=ON  (CABANA B?/AU AND (MICHAELIS
                A?/AU OR  MAGNANT G?/AU OR  SAYADA C?/AU))


=> d que nos L44

L44           0 SEA FILE=BIOSIS ABB=ON  PLU=ON  (MICHAELIS A?/AU AND  (
                MAGNANT G?/AU OR  SAYADA C?/AU))


=> d que nos L45

L45           0 SEA FILE=BIOSIS ABB=ON  PLU=ON  MAGNANT G?/AU AND  SAYADA
                C?/AU


=> d que nos L46

L3              STR
L5            1 SEA FILE=REGISTRY FAM FUL L3
L37         126 SEA FILE=BIOSIS ABB=ON  PLU=ON  L5
L38         138 SEA FILE=BIOSIS ABB=ON  PLU=ON  RIFALAZIL OR ABI 1648 OR
                ABI1648 OR KRM1648 OR KRM 1648
L39          32 SEA FILE=BIOSIS ABB=ON  PLU=ON  CABANA B?/AU
L40          67 SEA FILE=BIOSIS ABB=ON  PLU=ON  MICHAELIS A?/AU
L41           0 SEA FILE=BIOSIS ABB=ON  PLU=ON  MAGNANT G?/AU
L42          89 SEA FILE=BIOSIS ABB=ON  PLU=ON  SAYADA C?/AU
L46           2 SEA FILE=BIOSIS ABB=ON  PLU=ON  (L37 OR L38) AND (L39 OR L40
                OR L41 OR L42)


=> d que nos L128

L3              STR
L5            1 SEA FILE=REGISTRY FAM FUL L3
L37         126 SEA FILE=BIOSIS ABB=ON  PLU=ON  L5
L38         138 SEA FILE=BIOSIS ABB=ON  PLU=ON  RIFALAZIL OR ABI 1648 OR
                ABI1648 OR KRM1648 OR KRM 1648
L39          32 SEA FILE=BIOSIS ABB=ON  PLU=ON  CABANA B?/AU
L40          67 SEA FILE=BIOSIS ABB=ON  PLU=ON  MICHAELIS A?/AU
L41           0 SEA FILE=BIOSIS ABB=ON  PLU=ON  MAGNANT G?/AU
```

```
L42          89 SEA FILE=BIOSIS ABB=ON  PLU=ON  SAYADA C?/AU
L46           2 SEA FILE=BIOSIS ABB=ON  PLU=ON  (L37 OR L38) AND (L39 OR L40
                OR L41 OR L42)
L121            QUE  ABB=ON  PLU=ON  ?ATHERO? OR ?ARTER? OR ?CORONAR? OR
                ?CARDIO? OR ?CARDIAC? OR ?ISCHEM? OR STROKE? OR ?ISCHAEM?
                 OR ?BRAIN? OR ?CEREBR?
L122        138 SEA FILE=BIOSIS ABB=ON  PLU=ON  (L37 OR L38)
L123          2 SEA FILE=BIOSIS ABB=ON  PLU=ON  L122 AND L121
L124            QUE  ABB=ON  PLU=ON  ?HEART? OR ?CARDIAL OR ANGINA? OR ?C
                LAUDIC? OR ?GANGREN? OR ?NECROS? OR ?MESENT?
L125          5 SEA FILE=BIOSIS ABB=ON  PLU=ON  L122 AND L124
L126            QUE  ABB=ON  PLU=ON  ?ARTERIT? OR ?AORTIT? OR HORTON?
L127          0 SEA FILE=BIOSIS ABB=ON  PLU=ON  L122 AND L126
L128          0 SEA FILE=BIOSIS ABB=ON  PLU=ON  L46 AND (L123 OR L125 OR L127)


=> s L43-L46 or L128

L158          2 (L43 OR L44 OR L45 OR L46) OR L128

=> file uspatfull

FILE 'USPATFULL' ENTERED AT 11:54:16 ON 06 MAR 2006
CA INDEXING COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 2 Mar 2006 (20060302/PD)
FILE LAST UPDATED: 2 Mar 2006 (20060302/ED)
HIGHEST GRANTED PATENT NUMBER: US7007305
HIGHEST APPLICATION PUBLICATION NUMBER: US2006048257
CA INDEXING IS CURRENT THROUGH 28 Feb 2006 (20060228/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 2 Mar 2006 (20060302/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2005


=> d que nos L143

L140          3 SEA FILE=USPATFULL ABB=ON  PLU=ON  (CABANA B?/AU AND (MICHAELIS
                 A?/AU OR  MAGNANT G?/AU OR  SAYADA C?/AU))
L141          5 SEA FILE=USPATFULL ABB=ON  PLU=ON  (MICHAELIS A?/AU AND  (
                MAGNANT G?/AU OR  SAYADA C?/AU))
L142          2 SEA FILE=USPATFULL ABB=ON  PLU=ON  MAGNANT G?/AU AND  SAYADA
                C?/AU
L143          7 SEA FILE=USPATFULL ABB=ON  PLU=ON  (L140 OR L141 OR L142)


=> d que nos L144

L3              STR
L5            1 SEA FILE=REGISTRY FAM FUL L3
L132         21 SEA FILE=USPATFULL ABB=ON  PLU=ON  L5
L133         38 SEA FILE=USPATFULL ABB=ON  PLU=ON  RIFALAZIL OR ABI 1648 OR
                ABI1648 OR KRM1648 OR KRM 1648
L136          3 SEA FILE=USPATFULL ABB=ON  PLU=ON  CABANA B?/AU
L137         55 SEA FILE=USPATFULL ABB=ON  PLU=ON  MICHAELIS A?/AU
L138         16 SEA FILE=USPATFULL ABB=ON  PLU=ON  MAGNANT G?/AU
L139         10 SEA FILE=USPATFULL ABB=ON  PLU=ON  SAYADA C?/AU
L144         10 SEA FILE=USPATFULL ABB=ON  PLU=ON  (L132 OR L133) AND (L136 OR
                L137 OR L138 OR L139)
```

```
=> d que nos L148

L3              STR
L5               1 SEA FILE=REGISTRY FAM FUL L3
L132            21 SEA FILE=USPATFULL ABB=ON  PLU=ON  L5
L133            38 SEA FILE=USPATFULL ABB=ON  PLU=ON  RIFALAZIL OR ABI 1648 OR
                   ABI1648 OR KRM1648 OR KRM 1648
L136             3 SEA FILE=USPATFULL ABB=ON  PLU=ON  CABANA B?/AU
L137            55 SEA FILE=USPATFULL ABB=ON  PLU=ON  MICHAELIS A?/AU
L138            16 SEA FILE=USPATFULL ABB=ON  PLU=ON  MAGNANT G?/AU
L139            10 SEA FILE=USPATFULL ABB=ON  PLU=ON  SAYADA C?/AU
L146               QUE  ABB=ON  PLU=ON  ?HEART? OR ?CARDIO? OR ?CARDIA? OR ?
                   ANGINA? OR STROKE? OR ?CEREBR? OR ?BRAIN? OR ?CLAUDIC? OR
                    GANGREN? OR ?ISCHEM? OR ?ISCHAEM?
L147            28 SEA FILE=USPATFULL ABB=ON  PLU=ON  (L132 OR L133) AND L146
L148             9 SEA FILE=USPATFULL ABB=ON  PLU=ON  L147 AND (L136 OR L137 OR
                   L138 OR L139)


=> d que nos L153

L3              STR
L5               1 SEA FILE=REGISTRY FAM FUL L3
L132            21 SEA FILE=USPATFULL ABB=ON  PLU=ON  L5
L133            38 SEA FILE=USPATFULL ABB=ON  PLU=ON  RIFALAZIL OR ABI 1648 OR
                   ABI1648 OR KRM1648 OR KRM 1648
L134        303236 SEA FILE=USPATFULL ABB=ON  PLU=ON  ?ARTER? OR ?ATHERO?
L135            13 SEA FILE=USPATFULL ABB=ON  PLU=ON  (L132 OR L133) AND L134
L136             3 SEA FILE=USPATFULL ABB=ON  PLU=ON  CABANA B?/AU
L137            55 SEA FILE=USPATFULL ABB=ON  PLU=ON  MICHAELIS A?/AU
L138            16 SEA FILE=USPATFULL ABB=ON  PLU=ON  MAGNANT G?/AU
L139            10 SEA FILE=USPATFULL ABB=ON  PLU=ON  SAYADA C?/AU
L153            10 SEA FILE=USPATFULL ABB=ON  PLU=ON  (L136 OR L137 OR L138 OR
                   L139) AND L135


=> d que nos L154

L3              STR
L5               1 SEA FILE=REGISTRY FAM FUL L3
L132            21 SEA FILE=USPATFULL ABB=ON  PLU=ON  L5
L133            38 SEA FILE=USPATFULL ABB=ON  PLU=ON  RIFALAZIL OR ABI 1648 OR
                   ABI1648 OR KRM1648 OR KRM 1648
L136             3 SEA FILE=USPATFULL ABB=ON  PLU=ON  CABANA B?/AU
L137            55 SEA FILE=USPATFULL ABB=ON  PLU=ON  MICHAELIS A?/AU
L138            16 SEA FILE=USPATFULL ABB=ON  PLU=ON  MAGNANT G?/AU
L139            10 SEA FILE=USPATFULL ABB=ON  PLU=ON  SAYADA C?/AU
L146               QUE  ABB=ON  PLU=ON  ?HEART? OR ?CARDIO? OR ?CARDIA? OR ?
                   ANGINA? OR STROKE? OR ?CEREBR? OR ?BRAIN? OR ?CLAUDIC? OR
                    GANGREN? OR ?ISCHEM? OR ?ISCHAEM?
L151             7 SEA FILE=USPATFULL ABB=ON  PLU=ON  (L132 OR L133) (P) L146
L154             3 SEA FILE=USPATFULL ABB=ON  PLU=ON  (L136 OR L137 OR L138 OR
                   L139) AND L151


=> s L143-L144 or L148 or L153-L154

L159            12 (L143 OR L144) OR L148 OR (L153 OR L154)
```

```
=> => dup rem L155 L156 L157 L158 L159
FILE 'HCAPLUS' ENTERED AT 11:55:27 ON 06 MAR 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'MEDLINE' ENTERED AT 11:55:27 ON 06 MAR 2006

FILE 'EMBASE' ENTERED AT 11:55:27 ON 06 MAR 2006
Copyright (c) 2006 Elsevier B.V. All rights reserved.

FILE 'BIOSIS' ENTERED AT 11:55:27 ON 06 MAR 2006
Copyright (c) 2006 The Thomson Corporation

FILE 'USPATFULL' ENTERED AT 11:55:27 ON 06 MAR 2006
CA INDEXING COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)
PROCESSING COMPLETED FOR L155
PROCESSING COMPLETED FOR L156
PROCESSING COMPLETED FOR L157
PROCESSING COMPLETED FOR L158
PROCESSING COMPLETED FOR L159
L160          21 DUP REM L155 L156 L157 L158 L159 (6 DUPLICATES REMOVED)
                 ANSWERS '1-11' FROM FILE HCAPLUS
                 ANSWER '12' FROM FILE BIOSIS
                 ANSWERS '13-21' FROM FILE USPATFULL

=> d ibib abs hitind hitstr L160 1-11; d iall L160 12; d ibib abs kwic hitstr L160
13-21

L160 ANSWER 1 OF 21  HCAPLUS  COPYRIGHT 2006 ACS on STN DUPLICATE 1
ACCESSION NUMBER:         2005:572595  HCAPLUS
DOCUMENT NUMBER:          143:71740
TITLE:                    Regimen for the administration of rifamycin-class
                          antibiotics
INVENTOR(S):              Michaelis, Arthur F.; Cabana, Bernard
                          E.
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 16 pp.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE       APPLICATION NO.         DATE
     ---------------      ----   --------   --------------------    --------
     US 2005143409         A1    20050630   US 2004-948608          20040923
     WO 2005030109         A2    20050407   WO 2004-US31317         20040924
     WO 2005030109         C2    20050825
     WO 2005030109         A3    20050714
         W:  AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG,
             BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR,
             CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, EG,
             ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL,
             IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ,
             LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX,
             MX, MZ, MZ, NA
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
```

EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-505855P P 20030924

AB The invention features an ascending dose regimen for the administration of rifamycin-class antibiotics. The dosing regimen can be used to treat bacterial infections and diseases related to infection.

IC ICM A61K031-4745
ICS A61K031-496; A61K031-5415

INCL 514291000; 514252130; 514224500

CC 1-5 (Pharmacology)
Section cross-reference(s): 2, 63

ST rifamycin **antibacterial** resistance tablet caplet bacterial infection sepsis CRP

IT **Atherosclerosis**
(-associated disease, prevention of; regimen for administration of rifamycin-class antibiotics)

IT **Inflammation**
Reproductive system, disease
(adnexitis; regimen for administration of rifamycin-class antibiotics)

IT Heart, disease
Inflammation
(endocarditis; regimen for administration of rifamycin-class antibiotics)

IT **Artery**
(foam cell; regimen for administration of rifamycin-class antibiotics)

IT **Antibacterial** agents
(non-rifamycin-class; regimen for administration of rifamycin-class antibiotics)

IT Ear, disease
Inflammation
(otitis, acute bacterial infection,; regimen for administration of rifamycin-class antibiotics)

IT **Inflammation**
Peritoneum, disease
(peritonitis; regimen for administration of rifamycin-class antibiotics)

IT Infection
Inflammation
Kidney, disease
(pyelonephritis; regimen for administration of rifamycin-class antibiotics)

IT **Antibacterial** agents
(quinolone; regimen for administration of rifamycin-class antibiotics)

IT Anti-**inflammatory** agents
Antibacterial agents
Anticoagulants
Antipyretics
Bacteremia
Chlamydia pneumoniae
Drug resistance
Enterococcus
Eubacteria
Firmicutes
Human
Hypolipemic agents
Macrophage
Meningitis
Moraxella catarrhalis

Platelet aggregation inhibitors
Staphylococcus aureus
Streptococcus pneumoniae
Streptococcus pyogenes
Surgery
(regimen for administration of rifamycin-class antibiotics)

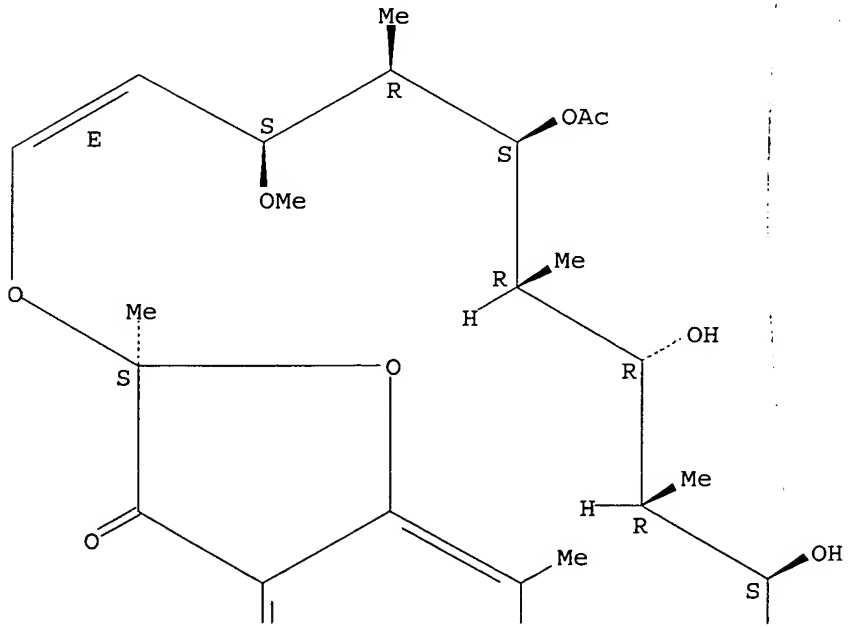
IT 50-02-2, Dexamethasone 50-24-8, Prednisolone 50-78-2, Aspirin 53-03-2, Prednisone 83-43-2, Methylprednisolone 114-07-8, Erythromycin 443-48-1, Metronidazole 13292-46-1, Rifampin 15687-27-1, Ibuprofen 26787-78-0, Amoxicillin 61379-65-5, Rifapentine 71125-38-7, Meloxicam 72559-06-9, Rifabutine 75330-75-5, Lovastatin 79902-63-9, Simvastatin 80621-81-4, Rifaximin 81093-37-0, Pravastatin 81103-11-9, Clarithromycin 83905-01-5, Azithromycin 93957-54-1, Fluvastatin 100986-85-4, Levofloxacin 112811-59-3, Gatifloxacin **129791-92-0**, **Rifalazil** 134523-00-5, Atorvastatin 145599-86-6, Cerivastatin 162011-90-7, Rofecoxib 169590-42-5, Celecoxib 287714-41-4, Rosuvastatin
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(regimen for administration of rifamycin-class antibiotics)

IT **129791-92-0**, **Rifalazil**
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(regimen for administration of rifamycin-class antibiotics)

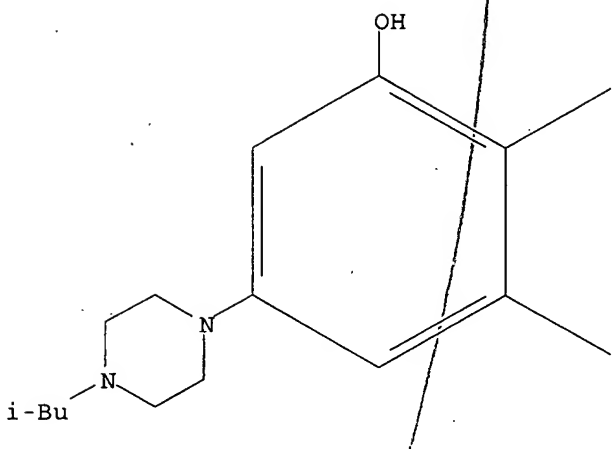
RN 129791-92-0 HCAPLUS
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

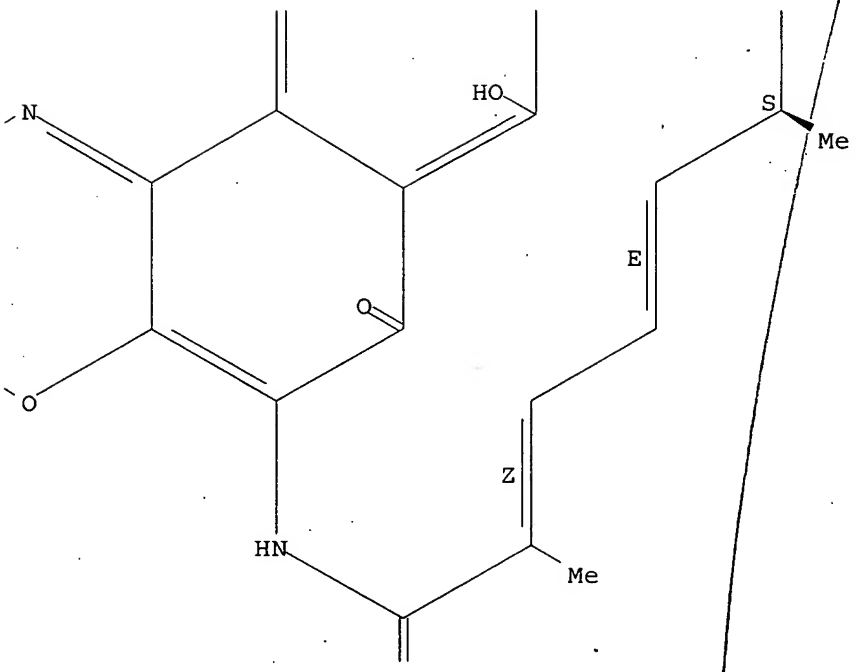
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

O

L160 ANSWER 2 OF 21 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2004:533649 HCAPLUS
DOCUMENT NUMBER: 141:47295
TITLE: Methods and compositions using rifamycins for treating and preventing ear infections

INVENTOR(S): **Michaelis, Arthur F.**
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 8 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004126414	A1	20040701	US 2003-734338		20031211
PRIORITY APPLN. INFO.:			US 2002-433428P	P	20021212

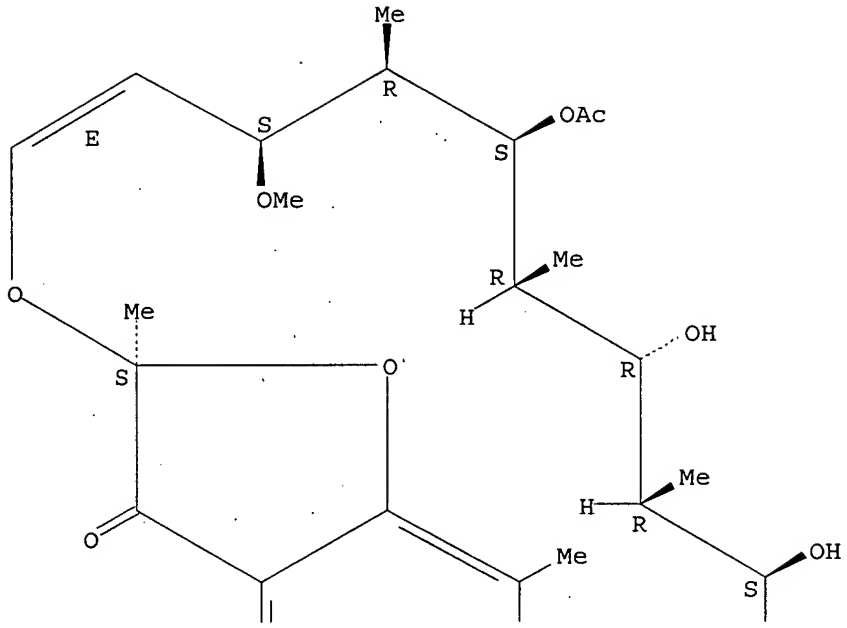
OTHER SOURCE(S): MARPAT 141:47295

AB The present invention relates to methods of treating, reducing, or preventing ear infections by topically administering a rifamycin of the invention to the ear of a patient. Infections amenable to treatment according to this invention include, for example, otitis media, otitis externa, or infections arising from surgery. The rifamycin is especially rifalazil.

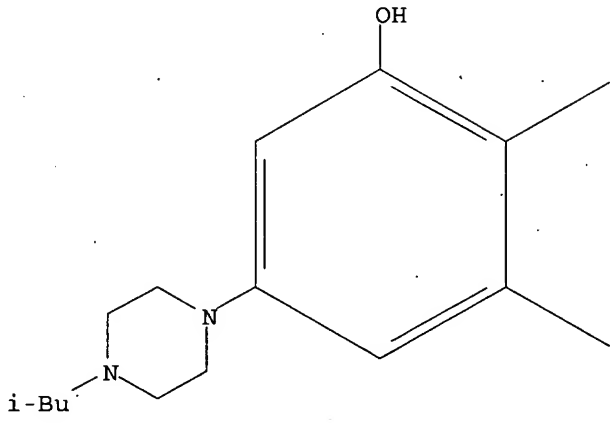
IC ICM A61K031-5415
ICS A61L015-16
INCL 424446000; 514224500
CC 1-5 (Pharmacology)
Section cross-reference(s): 63
IT 6998-60-3D, Rifamycin, compds. **129791-92-0**, Rifalazil
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rifamycins for treating and preventing bacterial ear infections)
IT **129791-92-0**, Rifalazil
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rifamycins for treating and preventing bacterial ear infections)
RN 129791-92-0 HCAPLUS
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

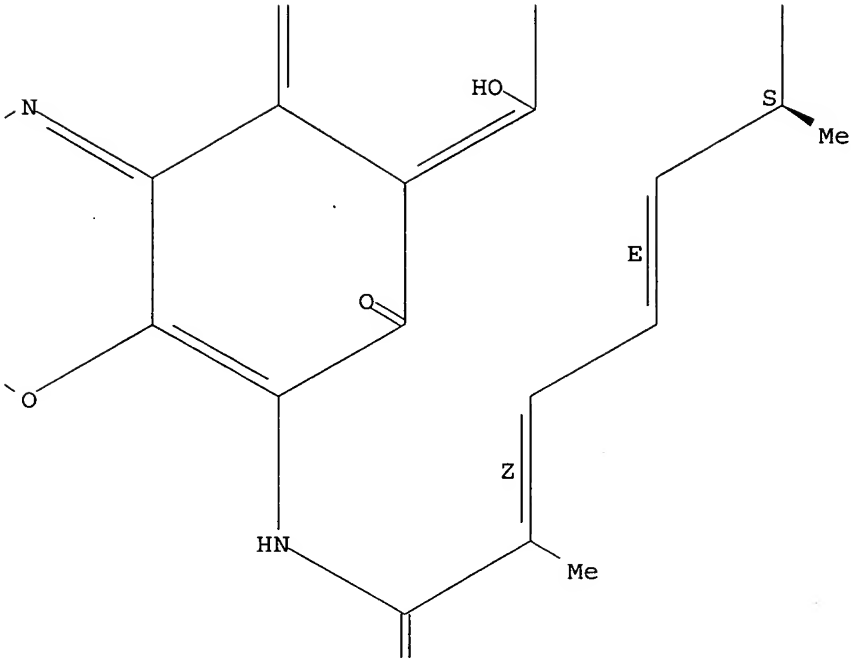
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

O

L160 ANSWER 3 OF 21 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2004:331758 HCAPLUS
DOCUMENT NUMBER: 140:335575
TITLE: Rifalazil and vancomycin antibacterial combination
INVENTOR(S): **Sayada, Chalom B.**
PATENT ASSIGNEE(S): Luxembourg
SOURCE: U.S. Pat. Appl. Publ., 17 pp., Cont.-in-part of U.S. Ser. No. 443,351.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004077533	A1	20040422	US 2003-651865	20030829
US 2003236265	A1	20031225	US 2003-443351	20030522
CA 2495144	AA	20040311	CA 2003-2495144	20030829
AU 2003268330	A1	20040319	AU 2003-268330	20030829
EP 1545453	A1	20050629	EP 2003-749288	20030829
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006501310	T2	20060112	JP 2004-569768	20030829
CA 2508823	AA	20040701	CA 2003-2508823	20031211

WO 2004054548 A1 20040701 WO 2003-US39585 20031211
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 2004176404 A1 20040909 US 2003-735344 20031211
EP 1575567 A1 20050921 EP 2003-796986 20031211
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

PRIORITY APPLN. INFO.:

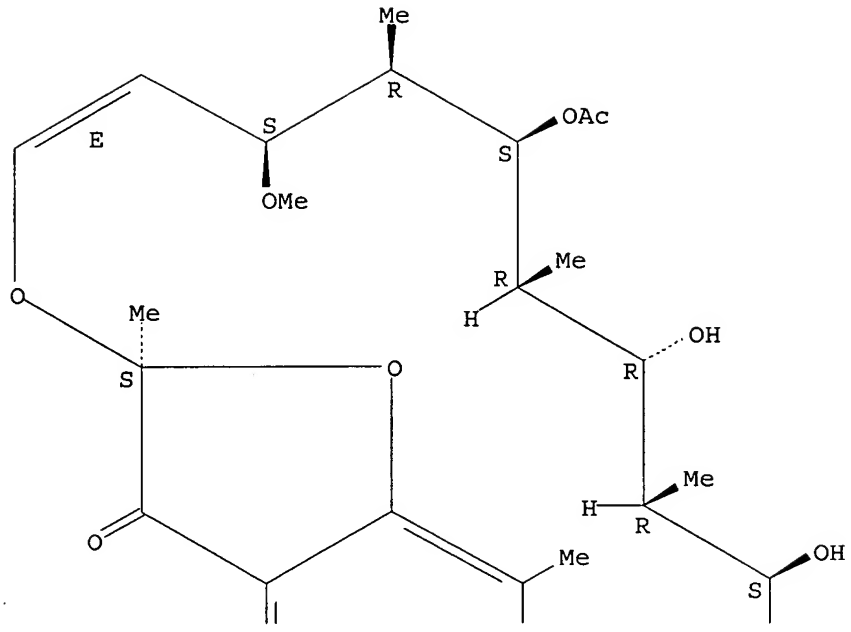
US 2002-382805P	P	20020523
US 2002-433379P	P	20021212
US 2003-444570P	P	20030203
US 2003-443351	A2	20030522
US 2002-406873P	P'	20020829
WO 2003-US27305	W	20030829
WO 2003-US39585	W	20031211

AB The invention features a rifamycin and vancomycin antibacterial combination. In treatment of log-phase Staphylococcus aureas cultures with rifalazil alone or in combination with vancomycin the combination were more effective with lower antibiotic concns. that rifalazil alone.

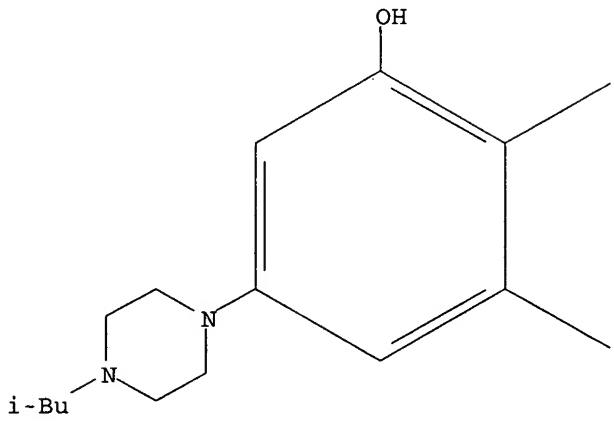
IC ICM A61K031-14
ICS A61K031-496
INCL 514008000; 514252130
CC 10-5 (Microbial, Algal, and Fungal Biochemistry)
Section cross-reference(s): 1, 63
IT 1404-90-6, Vancomycin 6998-60-3D, Rifamycin, derivs. **129791-92-0**, Rifalazil
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rifalazil and vancomycin antibacterial combination)
IT **129791-92-0**, Rifalazil
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rifalazil and vancomycin antibacterial combination)
RN 129791-92-0 HCAPLUS
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

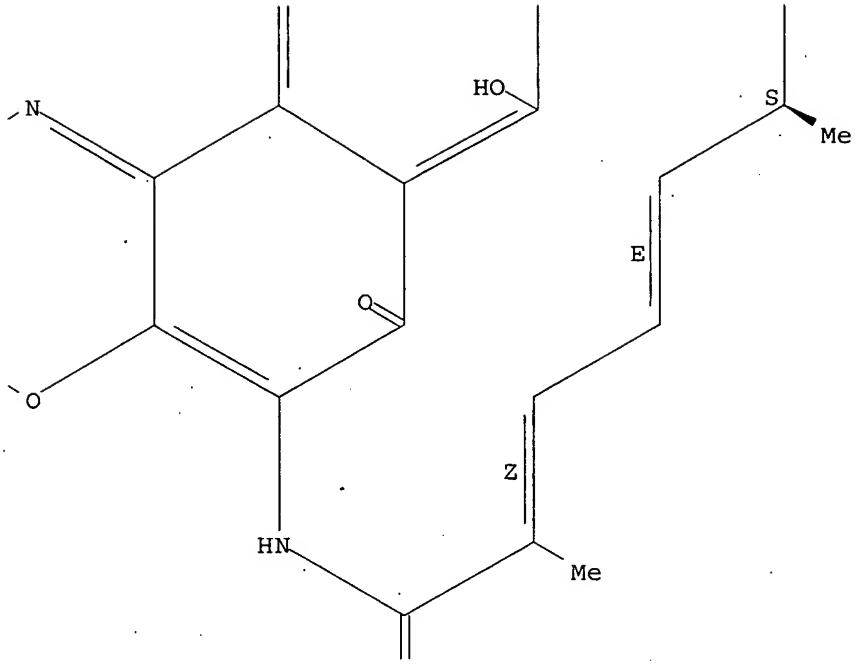
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

O

L160 ANSWER 4 OF 21 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 2004:848344 HCAPLUS
DOCUMENT NUMBER: 141:325234
TITLE: Rifalazil treats and prevents relapse of Clostridium difficile-associated diarrhea in hamsters
AUTHOR(S): Anton, Pauline M.; O'Brien, Michael; Kokkotou, Efi; Eisenstein, Barry; **Michaelis, Arthur**; Rothstein, David; Paraschos, Sophia; Kelly, Ciaran P.; Pothoulakis, Charalabos
CORPORATE SOURCE: Divisions of Gastroenterology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
SOURCE: Antimicrobial Agents and Chemotherapy (2004), 48(10), 3975-3979
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Although vancomycin and metronidazole effectively treat Clostridium difficile-associated diarrhea and colitis (CDAD), their use is associated with a high incidence of relapsing C. difficile infection. Rifalazil is a new benzoxazinorifamycin that possesses activity against Mycobacterium tuberculosis and gram-pos. bacteria. Here we compared rifalazil and vancomycin for effectiveness in preventing or treating clindamycin-induced

cecitis in a hamster model of CDAD. Golden Syrian hamsters were injected s.c. with clindamycin phosphate (10 mg/kg), followed 24 h later by C. difficile gavage. Hamsters received by gavage for 5 days vehicle, vancomycin (50 mg/kg), or rifalazil (20 mg/kg) either simultaneously with (prophylactic protocol) or 24 h after C. difficile administration (treatment protocol). While all vehicle-administered animals became moribund within 48 h of C. difficile administration, no rifalazil- or vancomycin-treated animals in either protocol showed signs of morbidity after 7 days. Ceca of rifalazil-treated animals showed absence of epithelial cell damage, significantly reduced congestion and edema, and less, but not statistically significantly less, neutrophil infiltration compared to those of vehicle-treated animals. In contrast, vancomycin-treated animals demonstrated severe epithelial cell damage and mildly reduced congestion and edema. Moreover, hamsters relapsed and tested C. difficile toxin pos. (by ELISA) 10 to 15 days after discontinuation of vancomycin treatment. None of the rifalazil-treated hamsters showed signs of disease or presence of toxins in their feces 30 days after discontinuation of treatment. Our results indicate that once daily rifalazil may be superior to vancomycin for curative treatment of CDAD.

CC 1-5 (Pharmacology)

IT **129791-92-0**, Rifalazil
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rifalazil treats and prevents relapse of Clostridium difficile-associated diarrhea in hamsters)

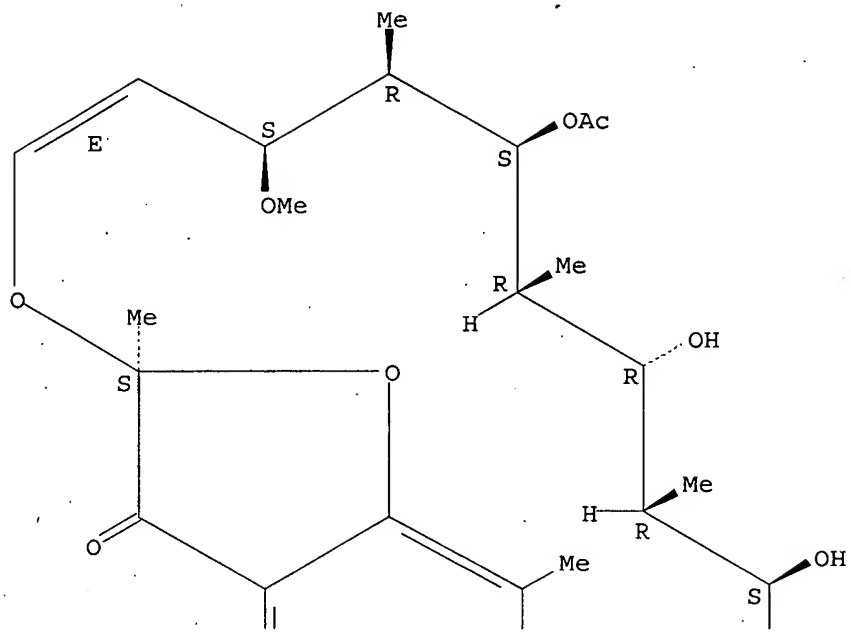
IT **129791-92-0**, Rifalazil
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rifalazil treats and prevents relapse of Clostridium difficile-associated diarrhea in hamsters)

RN 129791-92-0 HCAPLUS

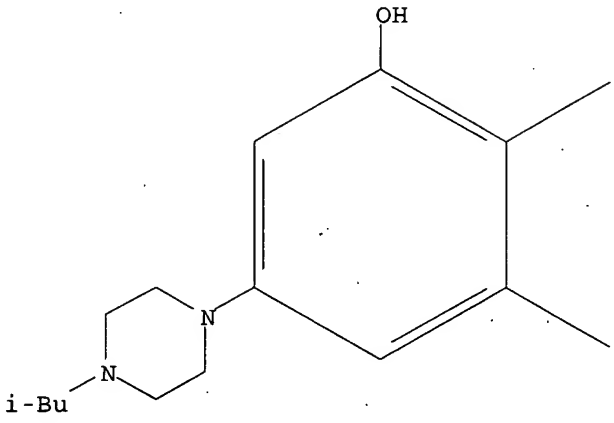
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

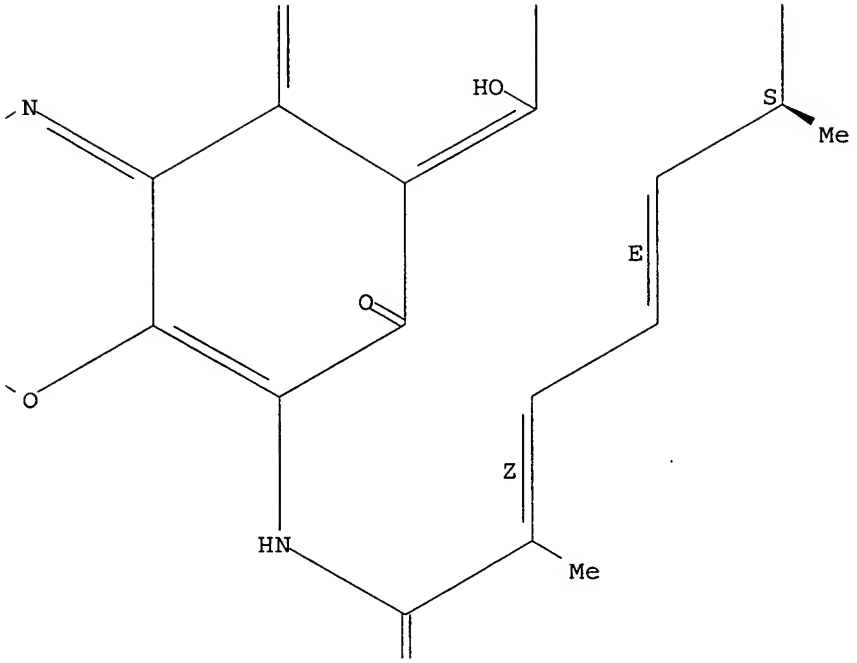
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

O

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L160 ANSWER 5 OF 21 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:300202 HCAPLUS
DOCUMENT NUMBER: 142:341945
TITLE: **Rifalazil** formulations
INVENTOR(S): **Michaelis, Arthur F.**
PATENT ASSIGNEE(S): Activbiotics, Inc., USA
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005030142	A2	20050407	WO 2004-US31542	20040927

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,

AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2005123602 A1 20050609 US 2004-950917 20040927
PRIORITY APPLN. INFO.: US 2003-506107P P 20030925

AB The invention features pharmaceutical compns. including **rifalazil** and a micelle-forming excipient and methods of use thereof. For example, PEG-35 castor oil, Pluronic F68, PEG 400, water, and **rifalazil** were mixed and filled into capsules to give 1 mg of **rifalazil** per capsule.

IC ICM A61K
CC 63-6 (Pharmaceuticals)
ST capsule **rifalazil** micelle forming excipient
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(C-reactive; oral formulations containing **rifalazil** in micelle-forming excipients)
IT **Inflammation**
Reproductive system, disease
(adnexitis, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Heart, disease
(**angina** pectoris, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Macrolides
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antibiotics, infection resistant to, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT **Artery**, disease
Inflammation
(**arteritis**, temporal, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Disease, animal
(arthropathy, infection, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Anti-**inflammatory** agents
Antibacterial agents
Anticoagulants
Antipyretics
Hypolipemic agents
Platelet aggregation inhibitors
(as addnl. drug; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Infection
Pneumonia
(bacterial, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Infection
(bone, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Drug delivery systems
(capsules, soft; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Drug delivery systems
(capsules; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Infection
(central nervous system, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)

IT **Ischemia**
(**cerebral**, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT **Artery**, disease
(**coronary**, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Infection
(cutaneous, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Joint, anatomical
(disease, infection, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT **Mesentery**
(disease, **ischemia**, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT **Atherosclerosis**
(diseases related to, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Heart, disease
Inflammation
(endocarditis, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Fatty acids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(esters, with lower alcs.; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Castor oil
Fatty acids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ethoxylated; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Necrosis
(**gangrene**, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Castor oil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydrogenated, ethoxylated; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Heart, disease
(infarction, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Abdomen, disease
Blood vessel, disease
Bone, disease
Central nervous system, disease
Digestive tract
Lung, disease
Respiratory system, disease
Skin, disease
Urogenital system, disease
Wound
(infection, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Enterococcus
Haemophilus influenzae
Moraxella catarrhalis
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae
(infections with, treatment of; oral formulations containing

rifalazil in micelle-forming excipients)
IT **Artery**, disease
(**intermittent claudication**, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Surfactants
(ionic; oral formulations containing **rifalazil** in micelle-forming excipients)
IT **Brain**, disease
(**ischemia**, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Antibiotics
(macrolide, infection resistant to, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT **Ischemia**
(**mesenteric**, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Drug bioavailability
Gelation agents
Human
(oral formulations containing **rifalazil** in micelle-forming excipients)
IT Polyoxyalkylenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral formulations containing **rifalazil** in micelle-forming excipients)
IT Ear, disease
Inflammation
(otitis media, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT **Inflammation**
Peritoneum, disease
(peritonitis, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Infection
(pulmonary, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Infection
Inflammation
Kidney, disease
(pyelonephritis, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT **Antibacterial** agents
(quinolone, infection resistant to, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Chlamydia pneumoniae
(reducing replication in macrophage by; oral formulations containing **rifalazil** in micelle-forming excipients)
IT **Artery**, disease
(renal, stenosis, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Brain, disease
(**stroke**, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Bacteremia
Meningitis
Pneumonia
Sepsis
(treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)
IT Infection

(urogenital, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)

IT Infection
(wound, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)

IT 50-02-2, Dexamethasone 50-24-8, Prednisolone 50-78-2, Aspirin 53-03-2, Prednisone 83-43-2, Methylprednisolone 114-07-8, Erythromycin 443-48-1, Metronidazole 15687-27-1, Ibuprofen 26787-78-0, Amoxicillin 71125-38-7, Meloxicam 75330-75-5, Lovastatin 79902-63-9, Simvastatin 81093-37-0, Pravastatin 81103-11-9, Clarithromycin 83905-01-5, Azithromycin 93957-54-1, Fluvastatin 100986-85-4, Levofloxacin 112811-59-3, Gatifloxacin 134523-00-5, Atorvastatin 145599-86-6, Cerivastatin 162011-90-7, Rofecoxib 169590-42-5, Celecoxib 287714-41-4, Rosuvastatin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as addnl. drug; oral formulations containing **rifalazil** in micelle-forming excipients)

IT 61-32-5, Methicillin 1404-90-6, Vancomycin 1406-05-9, Penicillin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(infection resistant to, treatment of; oral formulations containing **rifalazil** in micelle-forming excipients)

IT **129791-92-0, Rifalazil**
RL: **PKT (Pharmacokinetics); THU (Therapeutic use);**
BIOL (Biological study); USES (Uses)
(oral formulations containing **rifalazil** in micelle-forming excipients)

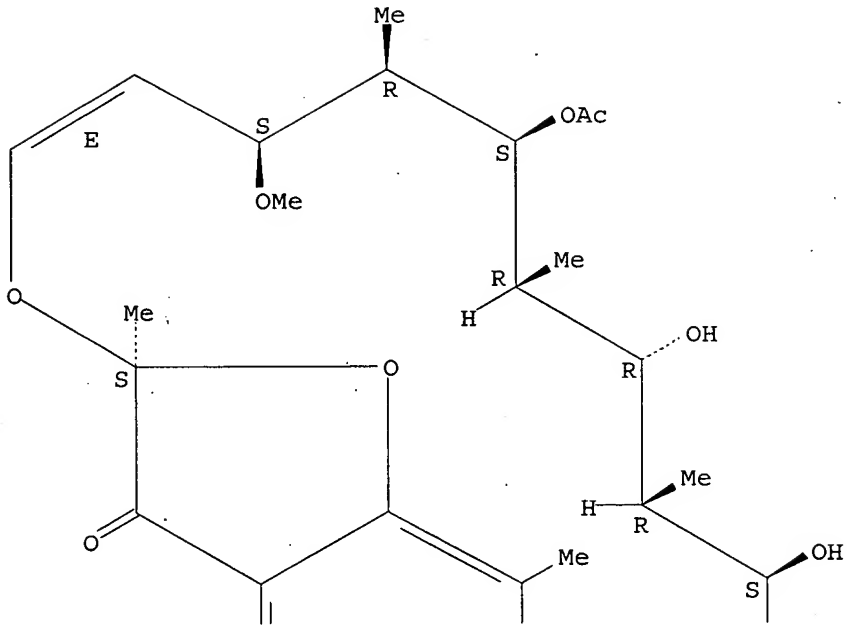
IT 57-55-6D, Propylene glycol, fatty acid esters 151-21-3, Sodium lauryl sulfate, biological studies 9004-99-3, Polyoxyethylene stearate 9005-63-4D, Polyoxyethylene sorbitan, fatty acid esters 12441-09-7D, Sorbitan, fatty acid esters 25322-68-3, Polyethylene glycol 25322-68-3D, Polyethylene glycol, fatty acid diesters 31694-55-0D, Polyoxyethylene glycerol, fatty acid esters 106392-12-5, Polyoxyethylenepolyoxypropylene block copolymer 691397-13-4, Pluronic F68
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral formulations containing **rifalazil** in micelle-forming excipients)

IT **129791-92-0, Rifalazil**
RL: **PKT (Pharmacokinetics); THU (Therapeutic use);**
BIOL (Biological study); USES (Uses)
(oral formulations containing **rifalazil** in micelle-forming excipients)

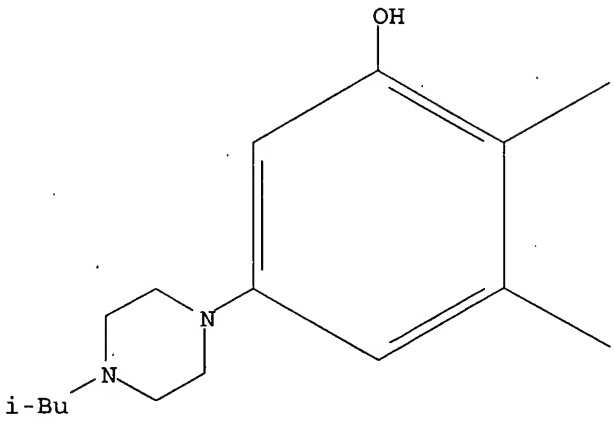
RN 129791-92-0 HCAPLUS
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

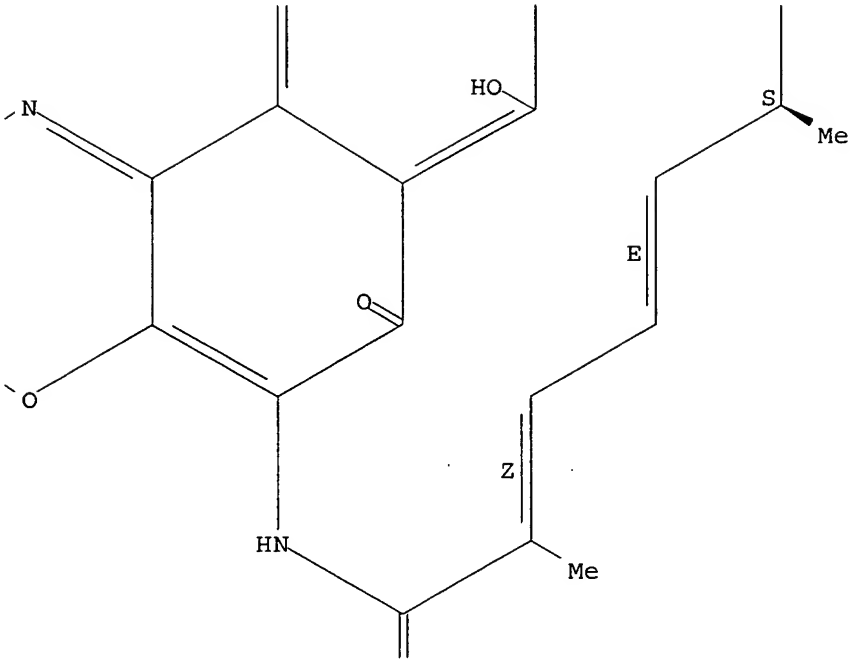
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

O

L160 ANSWER 6 OF 21 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:531310 HCAPLUS
DOCUMENT NUMBER: 141:47294
TITLE: Methods and compositions for treating and preventing ear infections
INVENTOR(S): **Michaelis, Arthur F.**
PATENT ASSIGNEE(S): Activbiotics, Inc., USA
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004054513	A2	20040701	WO 2003-US39532	20031211
WO 2004054513	A3	20050303		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,

BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-433428P P 20021212

OTHER SOURCE(S): MARPAT 141:47294

AB The invention relates to methods of treating, reducing, or preventing ear infections by topically administering a rifamycin of the invention to the ear of a patient. Infections amenable to treatment according to this invention include, for example, otitis media, otitis externa, or infections arising from surgery.

IC ICM A61K

CC 1-5 (Pharmacology)
Section cross-reference(s): 63

IT **129791-92-0**, Rifalazil
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods and compns. for treating and preventing ear infections)

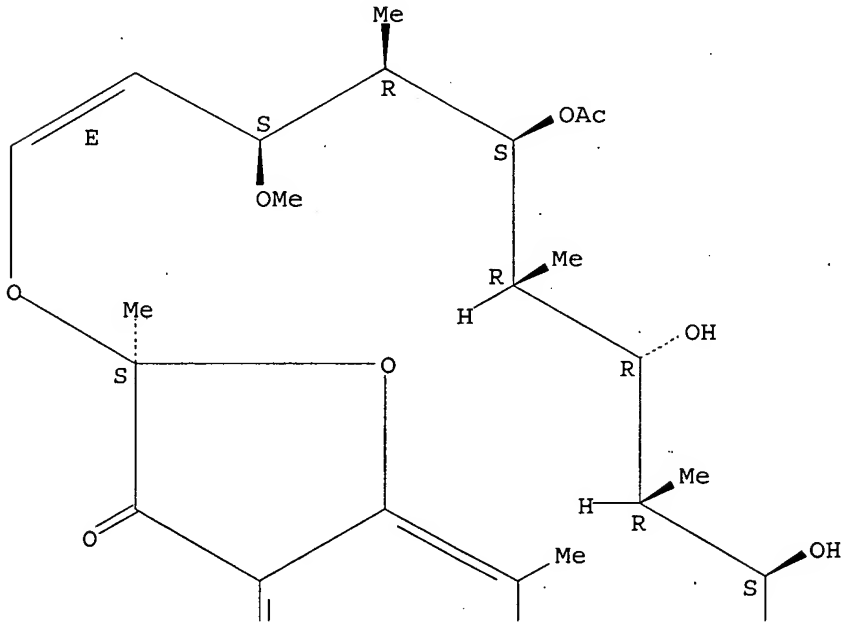
IT **129791-92-0**, Rifalazil
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods and compns. for treating and preventing ear infections)

RN 129791-92-0 HCAPLUS

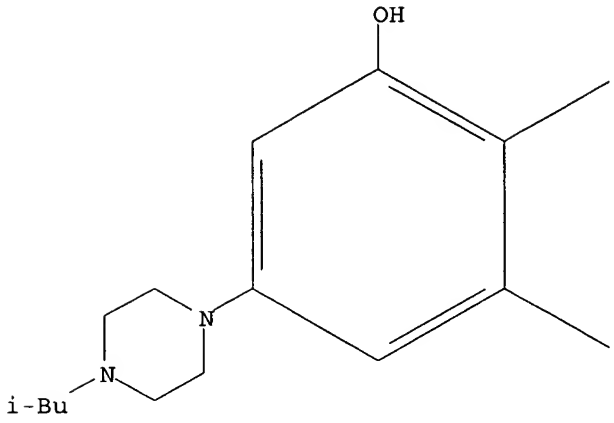
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

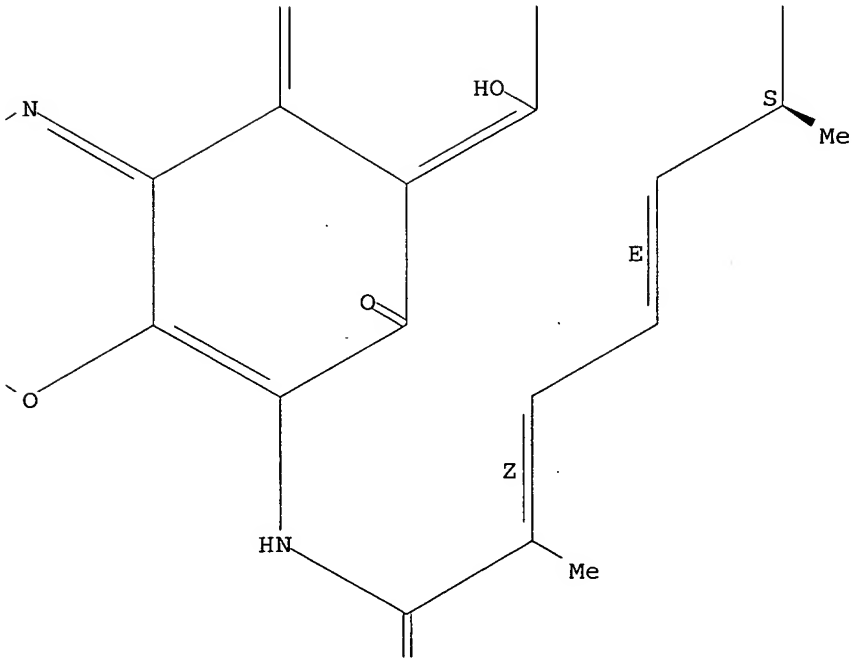
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

O

L160 ANSWER 7 OF 21 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:971882 HCAPLUS
DOCUMENT NUMBER: 140:19873
TITLE: Intravenous **rifalazil** formulation and

methods of use thereof

INVENTOR(S): **Michaelis, Arthur F.; Sayada, Chalom ; Cabana, Bernard E.**

PATENT ASSIGNEE(S): Activbiotics, Inc., USA

SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 5

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003101445	A1	20031211	WO 2003-US17273	20030603
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003239919	A1	20031219	AU 2003-239919	20030603
US 2004034021	A1	20040219	US 2003-453155	20030603
CA 2495144	AA	20040311	CA 2003-2495144	20030829
WO 2004019907	A1	20040311	WO 2003-US27305	20030829
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003268330	A1	20040319	AU 2003-268330	20030829
US 2004106590	A1	20040603	US 2003-652799	20030829
EP 1545453	A1	20050629	EP 2003-749288	20030829
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006501310	T2	20060112	JP 2004-569768	20030829
WO 2004041158	A2	20040521	WO 2003-US29647	20030923
WO 2004041158	A3	20040715		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004157840	A1	20040812	US 2003-668792	20030923
PRIORITY APPLN. INFO.:			US 2002-385532P P	20020603
			US 2002-406873P P	20020829
			US 2002-412958P P	20020923

US 2003-444570P P 20030203
WO 2003-US17273 W 20030603
WO 2003-US27305 W 20030829

AB The invention features i.v. dosage formulations of **rifalazil** and methods of treating disease by i.v. administration of **rifalazil.**

IC ICM A61K031-19
ICS A61K031-33; A61K031-34; A61K031-43; A61K031-56; A61K031-535

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 2

ST **rifalazil** intravenous formulation antibiotic

IT Proteins
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(C-reactive; i.v. **rifalazil** formulation and methods of use thereof)

IT Macrophage
(Chlamydia pneumoniae replication in; i.v. **rifalazil** formulation and methods of use thereof)

IT Castor oil
RL: MOA (Modifier or additive use); PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(PEG conjugates; i.v. **rifalazil** formulation and methods of use thereof)

IT Heart, disease
(**angina** pectoris; i.v. **rifalazil** formulation and methods of use thereof)

IT **Antiarteriosclerotics**
(**antiatherosclerotics**; i.v. **rifalazil** formulation and methods of use thereof)

IT **Artery**, disease
Inflammation
(**arteritis**; i.v. **rifalazil** formulation and methods of use thereof)

IT Infection
(bacterial; i.v. **rifalazil** formulation and methods of use thereof)

IT **Ischemia**
(**cerebral**; i.v. **rifalazil** formulation and methods of use thereof)

IT **Inflammation**
Uterus, disease
(cervicitis; i.v. **rifalazil** formulation and methods of use thereof)

IT Eye, disease
Inflammation
(conjunctivitis; i.v. **rifalazil** formulation and methods of use thereof)

IT **Artery**, disease
(**coronary**; i.v. **rifalazil** formulation and methods of use thereof)

IT Polyoxyalkylenes, biological studies
RL: POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(derivs.; i.v. **rifalazil** formulation and methods of use thereof).

IT Oviduct
(disease, salpingitis; i.v. **rifalazil** formulation and methods of use thereof)

IT Heart, disease

Inflammation
(endocarditis; i.v. **rifalazil** formulation and methods of use thereof)
IT Micelles
(excipients forming; i.v. **rifalazil** formulation and methods of use thereof)
IT **Artery**
(foam cell, Chlamydia pneumoniae replication in; i.v. **rifalazil** formulation and methods of use thereof)
IT Necrosis
(**gangrene**; i.v. **rifalazil** formulation and methods of use thereof)
IT Alzheimer's disease
Anaplasma
Anti-Alzheimer's agents
Anti-**inflammatory** agents
Antiarthritics
Antibiotic resistance
Antibiotics
Anticoagulants
Antidiabetic agents
Antitumor agents
Arthritis
Asthma
Atherosclerosis
Autoimmune disease
Bartonella
Brachiola connori
Brachiola vesicularum
Brucella
Burn
Candida
Chlamydia
Chlamydia pneumoniae
Cirrhosis
Coxiella burnetii
Cystic fibrosis
Diabetes mellitus
Ehrlichia
Ehrlichia ruminantium
Encephalitozoon
Enterococcus
Haemobartonella
Haemophilus influenzae
Histoplasma
Human
Hypolipemic agents
Infection
Kidney, disease
Leishmania
Lupus erythematosus
Meningitis
Microsporidia
Moraxella catarrhalis
Mycoplasma
Mycosis
Neoplasm
Nervous system, disease
Nosema
Osteoporosis

Plasmodium (malarial genus)
Platelet aggregation inhibitors
Psoriasis
Respiratory system, disease
Rickettsia
Septata intestinalis
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus pyogenes
Toxoplasma gondii
Trachipleistophora
Trypanosoma
Vittaforma
(i.v. **rifalazil** formulation and methods of use thereof)

IT Drug delivery systems
Prosthetic materials and Prosthetics
(implants, infection from implantation of; i.v. **rifalazil** formulation and methods of use thereof)

IT Heart, disease
(infarction; i.v. **rifalazil** formulation and methods of use thereof)

IT Firmicutes
Urogenital system, disease
(infection; i.v. **rifalazil** formulation and methods of use thereof)

IT Drug delivery systems
(injections, i.v.; i.v. **rifalazil** formulation and methods of use thereof)

IT **Artery**, disease
(**intermittent claudication**; i.v. **rifalazil** formulation and methods of use thereof)

IT Infection
(intracellular; i.v. **rifalazil** formulation and methods of use thereof)

IT **Brain**, disease
(**ischemia**; i.v. **rifalazil** formulation and methods of use thereof)

IT Infection
(protozoal; i.v. **rifalazil** formulation and methods of use thereof)

IT **Artery**
(renal, stenosis; i.v. **rifalazil** formulation and methods of use thereof)

IT **Inflammation**
(salpingitis; i.v. **rifalazil** formulation and methods of use thereof)

IT Drug delivery systems
(solns., aqueous; i.v. **rifalazil** formulation and methods of use thereof)

IT Brain, disease
(**stroke**; i.v. **rifalazil** formulation and methods of use thereof)

IT Infection
(urogenital; i.v. **rifalazil** formulation and methods of use thereof)

IT Hodgkin's disease
(venereum; i.v. **rifalazil** formulation and methods of use thereof)

IT Infection

(viral; i.v. **rifalazil** formulation and methods of use thereof)

IT 151-21-3, Sodium lauryl sulfate, biological studies 9004-99-3, Polyoxyl-40 stearate
RL: MOA (Modifier or additive use); PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(i.v. **rifalazil** formulation and methods of use thereof)

IT 50-02-2, Dexamethasone 50-24-8, Prednisolone 50-78-2, Aspirin 53-03-2, Prednisone 83-43-2, Methylprednisolone 114-07-8, Erythromycin 443-48-1, Metronidazole 15687-27-1, Ibuprofen 26787-78-0, Amoxicillin 71125-38-7, Meloxicam 75330-75-5, Lovastatin 79902-63-9, Simvastatin 81093-37-0, Pravastatin 81103-11-9, Clarithromycin 83905-01-5, Azithromycin 93957-54-1, Fluvastatin 100986-85-4, Levofloxacin 112811-59-3, Gatifloxacin 134523-00-5, Atorvastatin 145599-86-6, Cerivastatin 162011-90-7, Rofecoxib 169590-42-5, Celecoxib 287714-41-4, Rosuvastatin
RL: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(i.v. **rifalazil** formulation and methods of use thereof)

IT **129791-92-0**, **Rifalazil**
RL: PEP (Physical, engineering or chemical process); PYP (Physical process); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(i.v. **rifalazil** formulation and methods of use thereof)

IT 25322-68-3D, Polyethylene glycol, derivs.
RL: POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(i.v. **rifalazil** formulation and methods of use thereof)

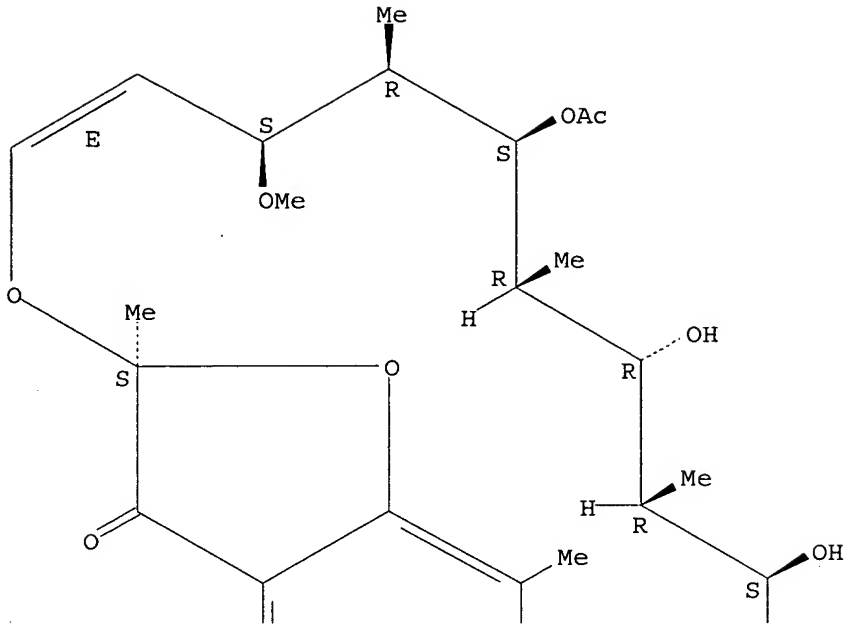
IT 9028-35-7
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors, statins; i.v. **rifalazil** formulation and methods of use thereof)

IT **129791-92-0**, **Rifalazil**
RL: PEP (Physical, engineering or chemical process); PYP (Physical process); **THU (Therapeutic use)**; BIOL (Biological study); PROC (Process); USES (Uses)
(i.v. **rifalazil** formulation and methods of use thereof)

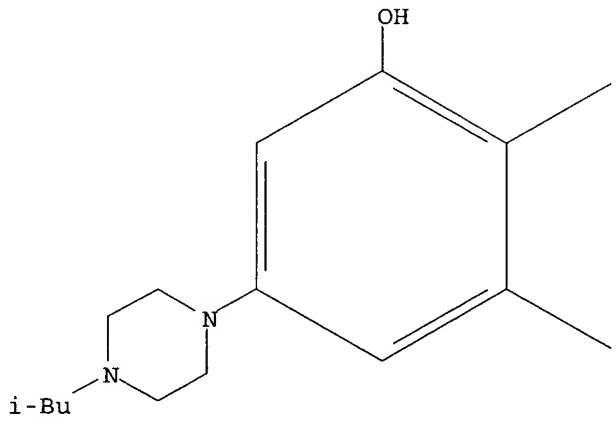
RN 129791-92-0 HCAPLUS
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

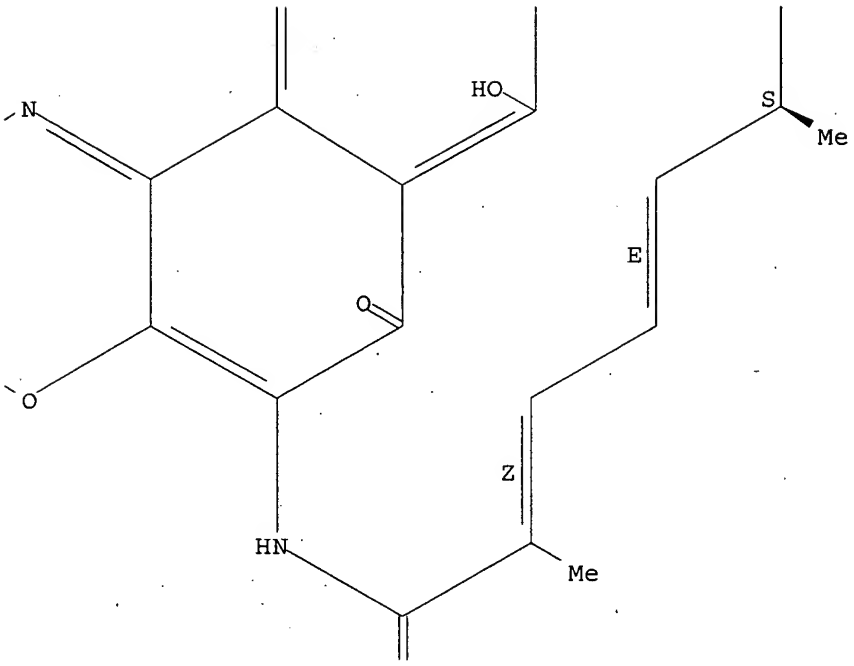
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

O

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L160 ANSWER 8 OF 21 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:950791 HCAPLUS
DOCUMENT NUMBER: 140:13017
TITLE: Methods using an antibiotic combination for treating infections of bacteria having multiplying and non-multiplying forms, as well as treating associated diseases
INVENTOR(S): **Sayada, Chalom**
PATENT ASSIGNEE(S): Activbiotics, Inc., USA
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003099217	A2	20031204	WO 2003-US16150	20030522
WO 2003099217	A3	20050324		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT,
TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2490062	AA	20031204	CA 2003-2490062	20030522
EP 1531828	A2	20050525	EP 2003-755429	20030522

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

PRIORITY APPLN. INFO.:	US 2002-382805P	P	20020523
	WO 2003-US16150	W	20030522

AB The invention discloses methods and compns. for treating non-multiplying forms of bacterial infections. The methods of the invention employ a rifamycin antibiotic and an antibiotic effective against the multiplying form of the bacterium.

IC ICM A61K

CC 1-5 (Pharmacology)
Section cross-reference(s): 63

IT **Antiarteriosclerotics**
(**antiatherosclerotics**; antibiotic combination for treating infections of bacteria having multiplying and non-multiplying forms, as well as treating associated diseases)

IT Anti-**inflammatory** agents
Antiarthritics
Antiasthmatics
Antibacterial agents
Antibiotic resistance
Antibiotics
Antidiabetic agents
Arthritis
Asthma
Atherosclerosis
Autoimmune disease
Cardiovascular agents
Chlamydia muridarum
Chlamydia pecorum
Chlamydia pneumoniae
Chlamydia suis
Chlamydia trachomatis
Chlamydophila abortus
Chlamydophila caviae
Chlamydophila felis
Chlamydophila psittaci
Clostridium perfringens
Diabetes mellitus
Drug delivery systems
Enterococcus faecalis
Enterococcus faecium
Inflammation
Neochlamydia hartmannellae
Parachlamydia acanthamoebae
Simkania negevensis
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus pyogenes
Waddlia chondrophila
(antibiotic combination for treating infections of bacteria having

multiplying and non-multiplying forms, as well as treating associated diseases)

IT **Inflammation**
Uterus, disease
(cervicitis; antibiotic combination for treating infections of bacteria having multiplying and non-multiplying forms, as well as treating associated diseases)

IT Eye, disease
Inflammation
(conjunctivitis; antibiotic combination for treating infections of bacteria having multiplying and non-multiplying forms, as well as treating associated diseases)

IT **Artery**, disease
(**coronary**; antibiotic combination for treating infections of bacteria having multiplying and non-multiplying forms, as well as treating associated diseases)

IT **Inflammation**
(salpingitis; antibiotic combination for treating infections of bacteria having multiplying and non-multiplying forms, as well as treating associated diseases)

IT 50-59-9, Cephaloridine 57-62-5, Chlortetracycline 57-92-1, Streptomycin, biological studies 60-54-8, Tetracycline 61-32-5, Methicillin 61-33-6, Penicillin G, biological studies 61-72-3, Cloxacillin 63-74-1, Sulfanilamide 66-79-5, Oxacillin 68-35-9, Sulfadiazine 69-53-4, Ampicillin 79-57-2, Oxytetracycline 85-73-4, Sulfathalidine 87-08-1, , Penicillin V 114-07-8, Erythromycin 127-33-3, Demeclocycline 127-69-5, Sulfisoxazole 147-52-4, Nafcillin 150-13-0 153-61-7, Cephalothin 154-21-2, Lincomycin 389-08-2, , Nalidixic acid 443-48-1, Metronidazole 564-25-0, Doxycycline 723-46-6, Sulfamethoxazole 738-70-5, Trimethoprim 914-00-1, Methacycline 1403-66-3, Gentamicin 1404-04-2, Neomycin 1404-90-6, Vancomycin 1406-11-7, Polymyxin 1695-77-8, Spectinomycin 3116-76-5, Dicloxacillin 4697-36-3, Carbenicillin 6998-60-3, Rifamycin 6998-60-3D, Rifamycin, derivs. 7542-37-2 8063-07-8, Kanamycin 10118-90-8, Minocycline 14698-29-4, ,Oxolinic acid 15686-71-2, Cephalexin 18323-44-9, Clindamycin 21593-23-7, , Cephapirin 25953-19-9, Cefazolin 26787-78-0, Amoxicillin 32385-11-8, Sisomicin 32986-56-4, Tobramycin 34444-01-4, Cefamandole 34493-98-6, Dibekacin 34787-01-4, Ticarcillin 35607-66-0, Cefoxitin 37091-66-0, Azlocillin 37517-28-5, Amikacin 38821-53-3, Cephradine 51481-65-3, Mezlocillin 53994-73-3, Cefaclor 55268-75-2, Cefuroxime 56391-56-1, Netilmicin 56796-20-4, Cefmetazole 58001-44-8 58152-03-7, Isepamicin 61036-62-2, , Teicoplanin 61477-96-1, Piperacillin 62893-19-0, Cefoperazone 63527-52-6, ,Cefotaxime 64221-86-9, Imipenem 66148-78-5, Temocillin 68373-14-8, Sulbactam 68401-81-0, Ceftizoxime 70458-92-3, Pefloxacin 70458-96-7, Norfloxacin 72558-82-8, Ceftazidime 73384-59-5, Ceftriaxone 74011-58-8, Enoxacin 76168-82-6, Ramoplanin 76470-66-1, Loracarbef 78110-38-0, Aztreonam 79350-37-1, Cefixime 79660-72-3, Fleroxacin 80210-62-4, Cefpodoxime 81103-11-9, Clarithromycin 82419-36-1, , Ofloxacin 83905-01-5, Azithromycin 84957-29-9, , Cefpirome 85721-33-1, Ciprofloxacin 88040-23-7, Cefepime 89786-04-9, Tazobactam 91832-40-5, Cefdinir 92665-29-7, Cefprozil 96036-03-2, Meropenem 97519-39-6, Ceftibuten 98079-51-7, Lomefloxacin 103060-53-3, Daptomycin 105956-97-6, Clinafloxacin 106560-14-9, Faropenem 108319-06-8, Temafloxacin 110871-86-8, Sparfloxacin 112362-50-2, Dalfopristin 112811-59-3, Gatifloxacin 119914-60-2, Grepafloxacin 120138-50-3, Quinupristin 127254-12-0, Sitafloxacin **129791-92-0**, **Rifalazil** 147059-72-1, Trovafloxacin 151096-09-2, Moxifloxacin 153832-46-3, Ertapenem 165800-03-3, Linezolid 171099-57-3, Oritavancin 171500-79-1, Dalbavancin

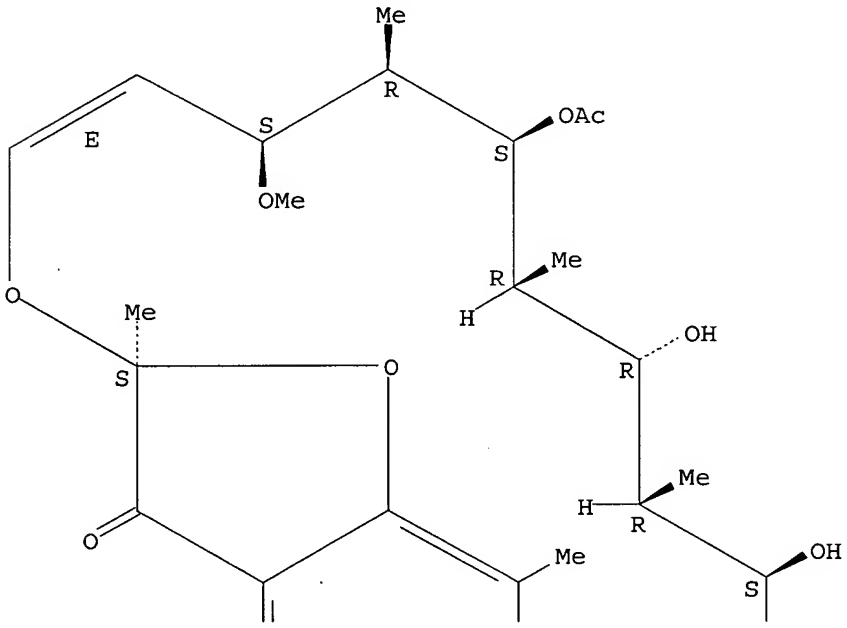
175463-14-6, Gemifloxacin 191114-48-4, Telithromycin 194804-75-6, Garenoxacin 205110-48-1, ABT-773 209467-52-7, BAL9141 220620-09-7, Tigecycline 252188-71-9 417702-79-5, AZD2563
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antibiotic combination for treating infections of bacteria having multiplying and non-multiplying forms, as well as treating associated diseases)

IT **129791-92-0, Rifalazil**
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(antibiotic combination for treating infections of bacteria having multiplying and non-multiplying forms, as well as treating associated diseases)

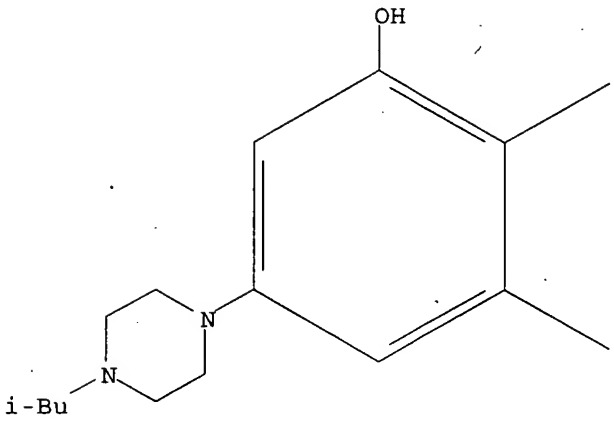
RN 129791-92-0 HCAPLUS
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

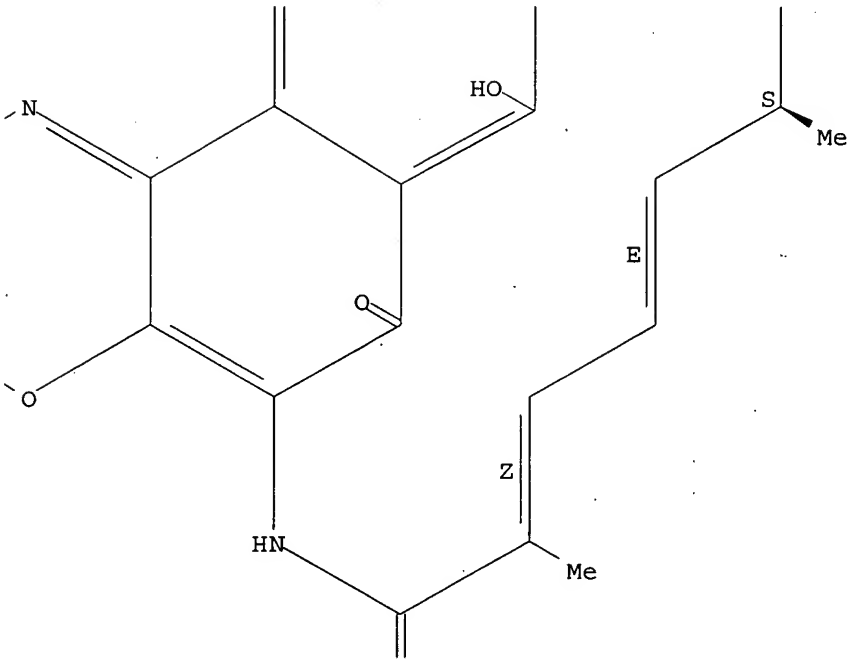
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

O

L160 ANSWER 9 OF 21 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:490991 HCAPLUS
DOCUMENT NUMBER: 139:57934
TITLE: Preparation of metal complexes and of rifamycin analog

formulations containing metal salts
INVENTOR(S): **Michaelis, Arthur F.**; Maudling, Hawkins V.; **Sayada, Chalom**; Eisenstein, Barry
PATENT ASSIGNEE(S): Activbiotics, Inc., USA
SOURCE: PCT Int. Appl., 88 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003051300	A2	20030626	WO 2002-US39888	20021212
WO 2003051300	A3	20031211		
WO 2003051300	C1	20040422		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004014750	A1	20040122	US 2002-318998	20021212
CA 2495144	AA	20040311	CA 2003-2495144	20030829
AU 2003268330	A1	20040319	AU 2003-268330	20030829
EP 1545453	A1	20050629	EP 2003-749288	20030829
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006501310	T2	20060112	JP 2004-569768	20030829
WO 2004041158	A2	20040521	WO 2003-US29647	20030923
WO 2004041158	A3	20040715		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004157840	A1	20040812	US 2003-668792	20030923

PRIORITY APPLN. INFO.:		
US 2001-341591P	P	20011213
US 2002-382805P	P	20020523
US 2002-385532P	P	20020603
US 2002-406873P	P	20020829
US 2002-412958P	P	20020923
US 2003-444570P	P	20030203
WO 2003-US27305	W	20030829

OTHER SOURCE(S): MARPAT 139:57934

AB The invention features compns. that include rifamycin analogs formulated with metal salts, metal complexes of rifamycin analogs, and methods for treating disease by using these compns. Thus, a rifamycin S analog prepared by a series of reactions starting from a thiazole derivative The drug had excellent **antibacterial** activity.

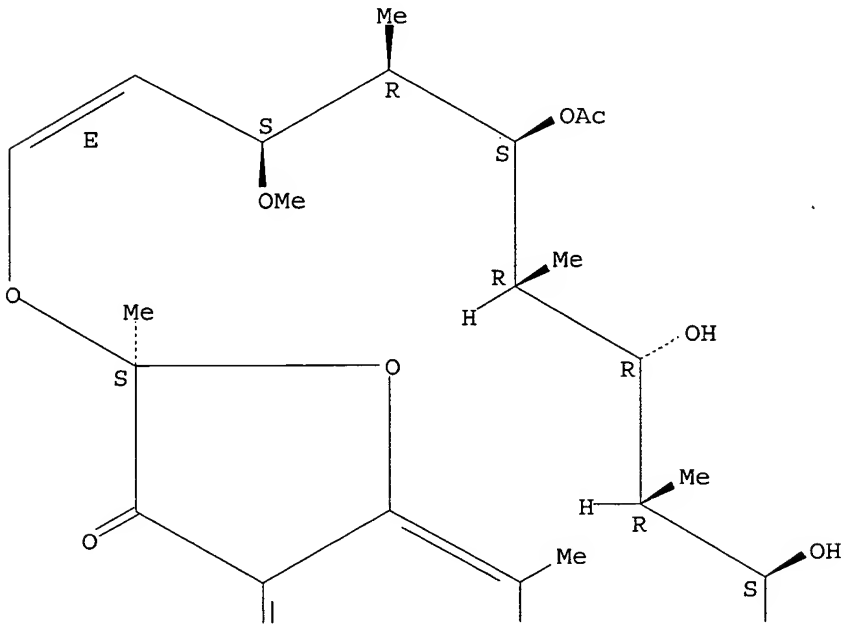
IC ICM A61K

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 26
IT Heart, disease
(**angina** pectoris; preparation of metal complexes and of rifamycin analog formulations containing metal salts)
IT **Artery**, disease
Inflammation
(**arteritis**, temporal; preparation of metal complexes and of rifamycin analog formulations containing metal salts)
IT **Ischemia**
(**cerebral**; preparation of metal complexes and of rifamycin analog formulations containing metal salts)
IT **Inflammation**
Uterus, disease
(cervicitis; preparation of metal complexes and of rifamycin analog formulation containing metal salts)
IT Eye, disease
Inflammation
(conjunctivitis; preparation of metal complexes and of rifamycin analog formulation containing metal salts)
IT **Artery**, disease
(**coronary**; preparation of metal complexes and of rifamycin analog formulations containing metal salts)
IT Necrosis
(**gangrene**; preparation of metal complexes and of rifamycin analog formulations containing metal salts)
IT **Artery**, disease
(**intermittent claudication**; preparation of metal complexes and of rifamycin analog formulations containing metal salts)
IT **Brain**, disease
(**ischemia**; preparation of metal complexes and of rifamycin analog formulations containing metal salts)
IT **Ischemia**
(mesentric; preparation of metal complexes and of rifamycin analog formulations containing metal salts)
IT Anti-**inflammatory** agents
(nonsteroidal; preparation of metal complexes and of rifamycin analog formulation containing metal salts)
IT Ear, disease
Inflammation
(otitis, acute or chronic; preparation of metal complexes and of rifamycin analog formulation containing metal salts)
IT Anti-**inflammatory** agents
Antianginal agents
Antibacterial agents
Anticoagulants
Antipyretics
Atherosclerosis
Drug resistance
Human
Macrophage
Platelet aggregation inhibitors
(preparation of metal complexes and of rifamycin analog formulations containing
metal salts)
IT **Artery**, disease
(renal, stenosis, temporal; preparation of metal complexes and of rifamycin analog formulations containing metal salts)
IT Brain, disease
(**stroke**; preparation of metal complexes and of rifamycin analog

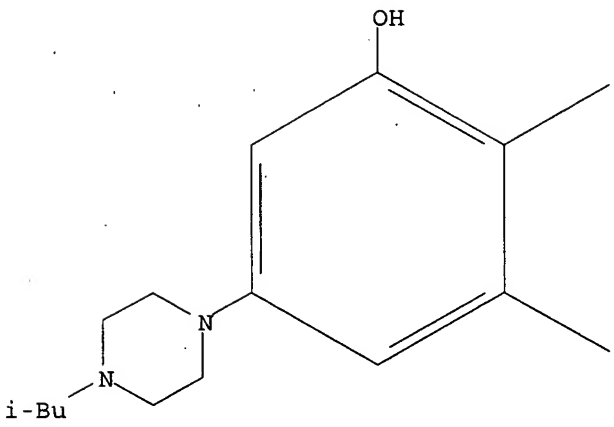
formulations containing metal salts)
IT 15438-31-0DP, Iron 2+, complex with **rifalazil**, biological studies **129791-92-0DP**, **Rifalazil**, complex with iron 536697-37-7P
RL: **PAC (Pharmacological activity)**; SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of metal complexes and of rifamycin analog formulations containing metal salts)
IT **129791-92-0**, **Rifalazil**
RL: RCT (Reactant); **THU (Therapeutic use)**; BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(preparation of metal complexes and of rifamycin analog formulations containing metal salts)
IT **129791-92-0DP**, **Rifalazil**, complex with iron
RL: **PAC (Pharmacological activity)**; SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of metal complexes and of rifamycin analog formulations containing metal salts)
RN 129791-92-0 HCAPLUS
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

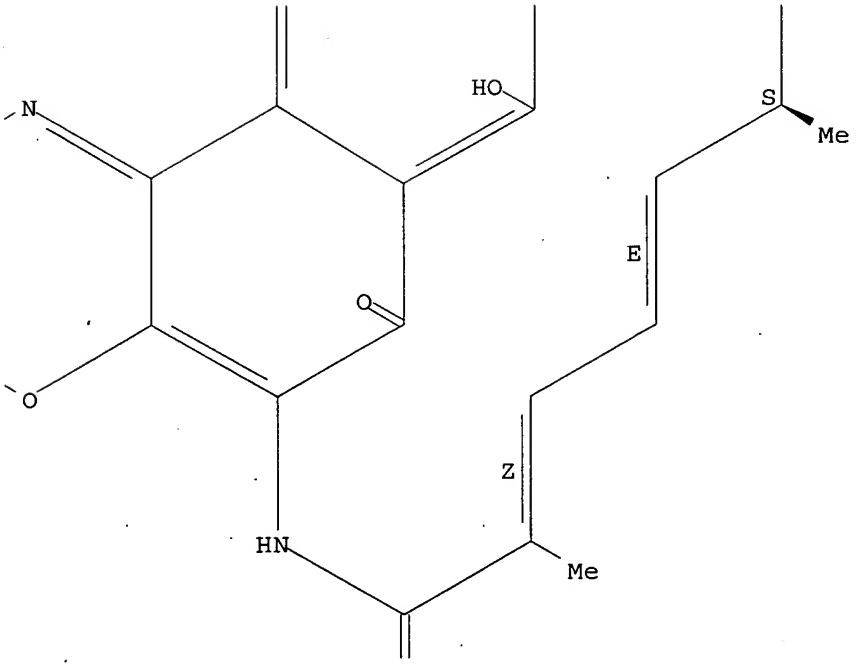
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

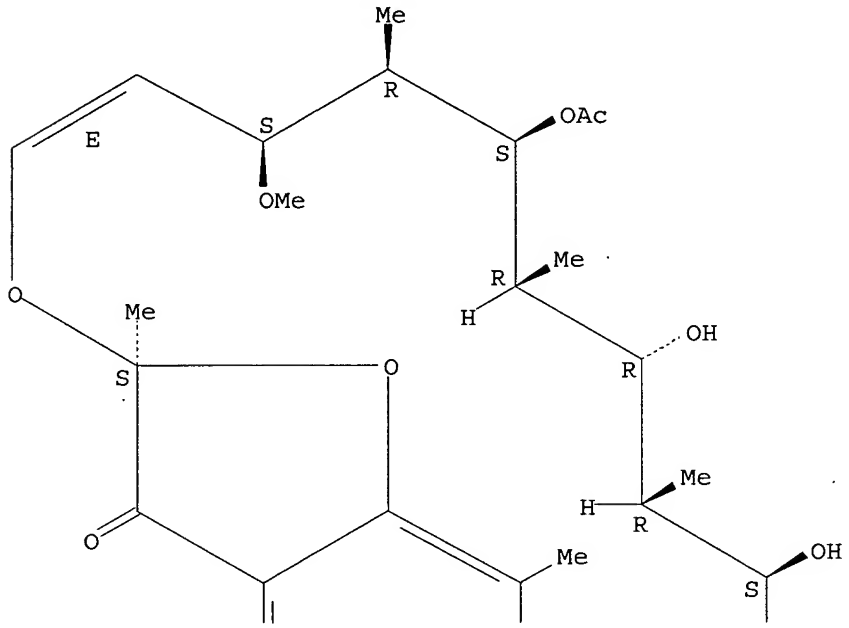
O

IT **129791-92-0, Rifalazil**
RL: RCT (Reactant); **THU (Therapeutic use)**; BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(preparation of metal complexes and of rifamycin analog formulations containing

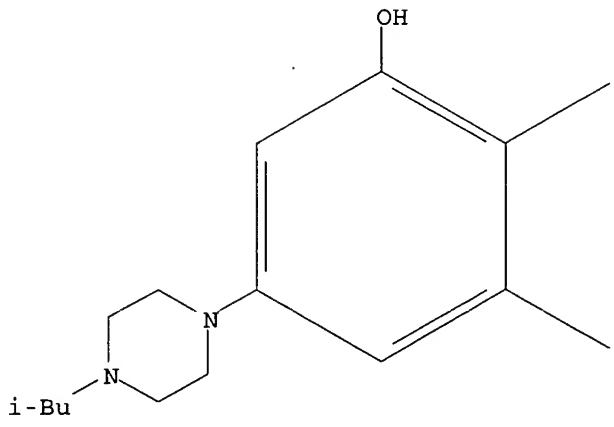
metal salts)
RN 129791-92-0 HCAPLUS
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

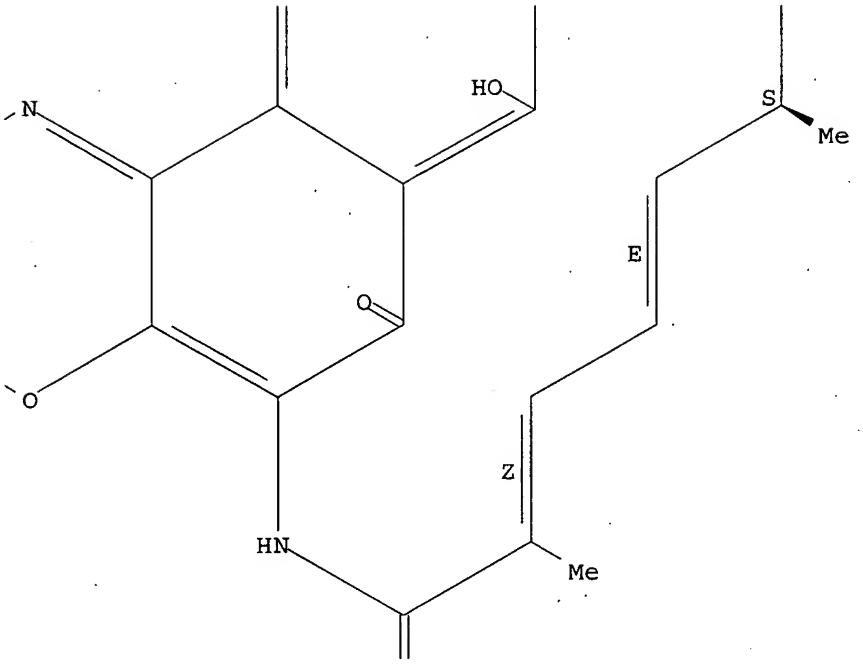
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

O

L160 ANSWER 10 OF 21 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:490990 HCAPLUS
DOCUMENT NUMBER: 139:57933
TITLE: Sulfhydryl rifamycins and their uses
INVENTOR(S): **Michaelis, Arthur F.**; Maulding, Hawkins V.; **Sayada, Chalom**; Einsenstein, Barry; Gleiss, William B.; Raker, Joseph
PATENT ASSIGNEE(S): Activbiotics, Inc., USA
SOURCE: PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003051299	A2	20030626	WO 2002-US39887	20021212
WO 2003051299	A3	20031224		
WO 2003051299	C1	20040422		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,

UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004014749	A1	20040122	US 2002-318582	20021212
CA 2495144	AA	20040311	CA 2003-2495144	20030829
AU 2003268330	A1	20040319	AU 2003-268330	20030829
EP 1545453	A1	20050629	EP 2003-749288	20030829

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

JP 2006501310	T2	20060112	JP 2004-569768	20030829
WO 2004041158	A2	20040521	WO 2003-US29647	20030923
WO 2004041158	A3	20040715		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004157840	A1	20040812	US 2003-668792	20030923

PRIORITY APPLN. INFO.:

US 2001-341130P	P	20011213
US 2002-382805P	P	20020523
US 2002-385532P	P	20020603
US 2002-406873P	P	20020829
US 2002-412958P	P	20020923
US 2003-444570P	P	20030203
WO 2003-US27305	W	20030829

OTHER SOURCE(S): MARPAT 139:57933

AB Compns. comprising sulfhydryl rifamycin compds., methods of making these compns., and methods for treating microbial infections using these compns. are described. A sulfhydryl rifamycin compound may be administered in conjunction with one or more addnl. agents, such as anti-inflammatory agents, antibacterial agents, platelet aggregation inhibitors, antipyretics, proton pump inhibitors, or lipid lowering agents. The addnl. therapeutic agent may be present in the same or different pharmaceutical compns. as the sulfhydryl rifamycin compound

IC ICM A61K
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 10, 26

L160 ANSWER 11 OF 21 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:434309 HCAPLUS
DOCUMENT NUMBER: 139:26617
TITLE: Rifamycin derivatives for drug targeting
INVENTOR(S): **Michaelis, Arthur F.**; Maulding, Hawkins V.; **Sayada, Chalom**; Zha, Congxiang
PATENT ASSIGNEE(S): Activbiotics, Inc., USA
SOURCE: PCT Int. Appl., 113 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2003045319	A2	20030605	WO 2002-US37745	20021121
WO 2003045319	A3	20031030		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2465846	AA	20030605	CA 2002-2465846	20021121
US 2004063718	A1	20040401	US 2002-302409	20021121
EP 1453837	A2	20040908	EP 2002-795669	20021121
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
JP 2005510534	T2	20050421	JP 2003-546824	20021121
PRIORITY APPLN. INFO.:			US 2001-332264P	P 20011121
			US 2002-358881P	P 20020222
			WO 2002-US37745	W 20021121

OTHER SOURCE(S): MARPAT 139:26617

AB The invention features a method of delivering a drug to a diseased cell by linking the drug to a rifamycin derivative, compns. that include drug-rifamycin conjugates, and methods for treating disease using those composition A method of treating or preventing diseases comprises the step of administering conjugates of formula (A)-(L)-(B) (A = rifamycin derivative; B = drug, e.g., antimicrobial or anti-**inflammatory** drug such is isoniazid, ethambutol, azithromycin, pyrazinamide, p-aminosalicylic acid, cycloserine, detoprofen, diclofenac, ibuprofen, etc.; L = linker). For example, preparation of ABI 0029, a zero-length linker conjugate of **rifalazil** and isonicotinic acid was presented. Conjugation to **rifalazil** modifies the biodistribution of isonicotinic acid in a manner that can enhance its antimicrobial activity.

IC ICM A61K

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 26

ST rifamycin deriv drug conjugate targeting antimicrobial **antiinflammatory**

IT **Antiarteriosclerotics**
(**antiatherosclerotics**; preparation of drug conjugate with rifamycin derivative as targeting moiety)

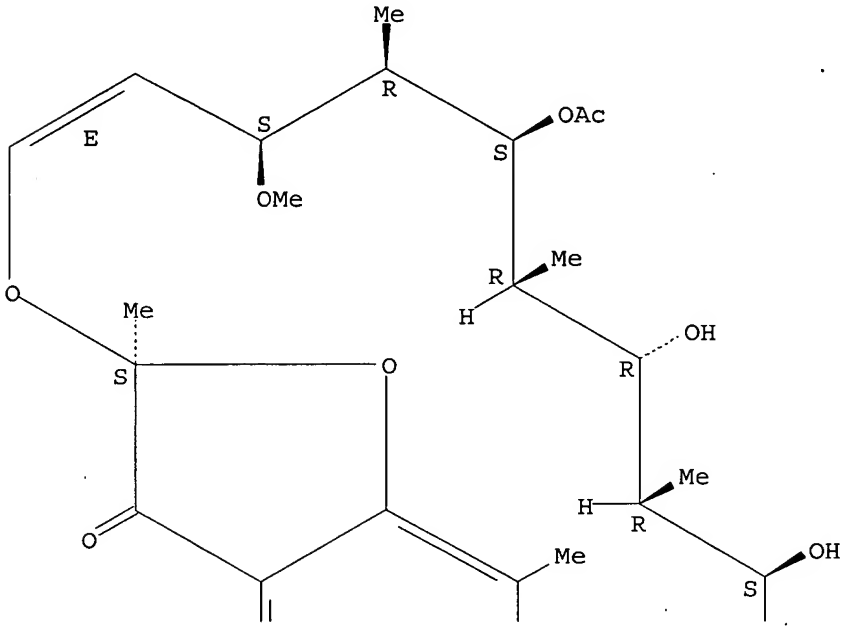
IT Anti-**inflammatory** agents
Antibacterial agents
Anticoagulants
Antimicrobial agents
Antiviral agents
Atherosclerosis
Fungicides
Hypolipemic agents
Platelet aggregation inhibitors
Protozoacides
(preparation of drug conjugate with rifamycin derivative as targeting moiety)

IT 77-76-9, 2,2-Dimethoxypropane 14254-57-0, Isonicotinoyl chloride 39178-35-3, Isonicotinoyl chloride hydrochloride **129791-92-0**, **Rifalazil**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of drug conjugate with rifamycin derivative as targeting moiety)

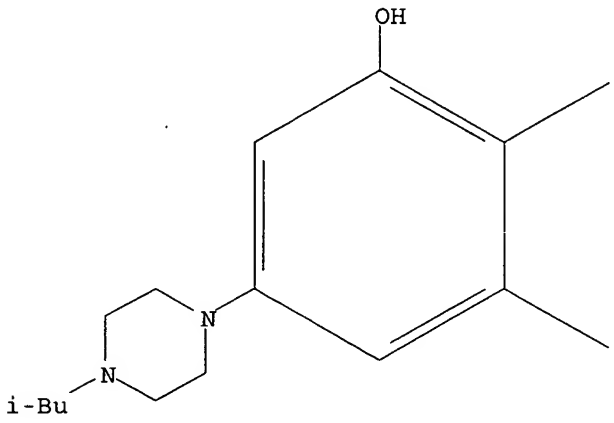
IT **129791-92-0, Rifalazil**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of drug conjugate with rifamycin derivative as targeting moiety)
RN 129791-92-0 HCAPLUS
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

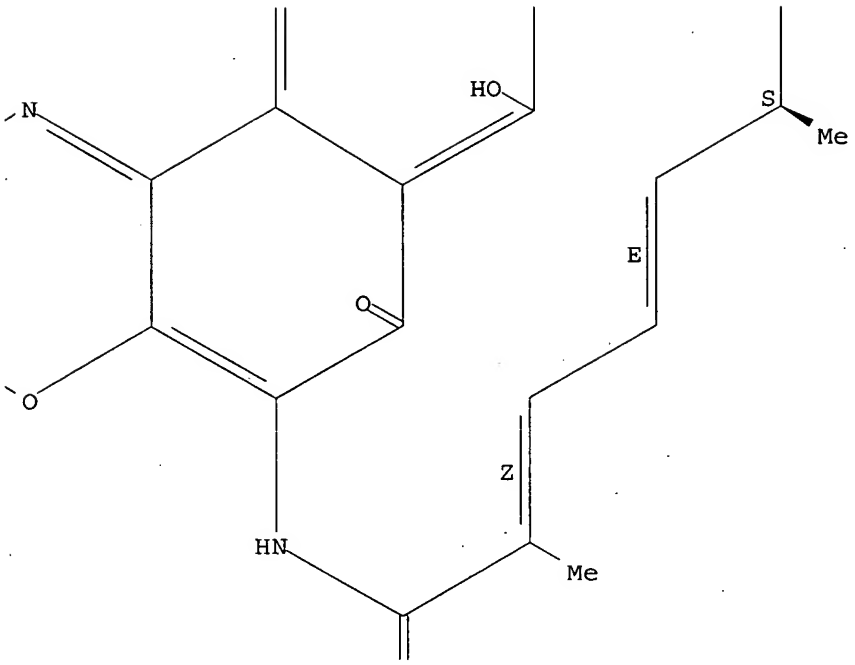
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

O

L160 ANSWER 12 OF 21 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:23910 BIOSIS
DOCUMENT NUMBER: PREV200400025319
TITLE: **Rifalazil** and derivative compounds exhibit very potent in vivo activity against Staphylococcus aureus in a mouse septicemia model system.
AUTHOR(S): Fernandes, D. [Reprint Author]; Sirokman, K. [Reprint Author]; Hazlett, C.; Gwathmey, J. K. [Reprint Author]; Van Duzer, J.; Brown, K.; **Michaelis, A. F.**; Rothstein, D. M.
CORPORATE SOURCE: Gwathmey, Inc., Cambridge, MA, USA
SOURCE: Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, (2003) Vol. 43, pp. 44. print. Meeting Info.: 43rd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, IL, USA. September 14-17, 2003. American Society for Microbiology.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Dec 2003
Last Updated on STN: 31 Dec 2003

ABSTRACT:Background: **Rifalazil** and rifampin are ansamycins with strong activity against Staphylococcus aureus in vitro. However, ***rifalazil*** efficacy had never been tested previously by intravenous (IV) administration. In this series of experiments, rifampin, **rifalazil**, and derivatives of **rifalazil** were tested for efficacy by both IV and oral administration. Methods: The mouse septicemia model utilizing the Staphylococcus aureus Smith isolate, inoculated into mice by intraperitoneal injection was utilized as described previously (W. J. Weiss, et al. Antimicrob. Agents Chemother. (1999) 43:460-464). In the absence of antibiotic intervention, most mice died in one day and all within three days. Results: The relative activities of three compounds, rifampin, ***rifalazil*** , and ABI-1131, a derivative of **rifalazil**, is given. All three compounds show potent in vitro activity, and correspondingly strong IV activity in the animal model system. The ratio of the IV and oral ED50 provides an approximation of the effective bioavailability of the compounds, approximates 50% for rifampin and **rifalazil**, but is considerably lower for compound ABI-1131. Conclusion: Rifampin, **rifalazil**, and compound ABI-1131 all show good correspondence between potent in vitro activity and strong IV activity in vivo. It is interesting that the replacement of the N- isobutyl piperazine group in **rifalazil** with the N-methyl piperazine moiety in ABI-1131 results in increased potency both in vitro and in vivo when administered IV, but diminished effective bioavailability.

CONCEPT CODE:
General biology - Symposia, transactions and proceedings 00520
Biochemistry studies - General 10060
Pathology - Therapy 12512
Pharmacology - General 22002
Physiology and biochemistry of bacteria 31000
Medical and clinical microbiology - General and methods 36001
Medical and clinical microbiology - Bacteriology 36002
Chemotherapy - General, methods and metabolism 38502
Chemotherapy - Antibacterial agents 38504

INDEX TERMS:
Major Concepts
Infection; Pharmacology

INDEX TERMS:
Diseases
septicemia: bacterial disease, infectious disease
Septicemia (MeSH)

INDEX TERMS:
Chemicals & Biochemicals
ABI-1131: antibacterial-drug, antiinfective-drug, derivative, intravenous administration, oral administration; **rifalazil**: antibacterial-drug, antiinfective-drug, derivative compounds, intravenous administration, oral administration; rifampin: enzyme inhibitor-drug, intravenous administration, oral administration

ORGANISM:
Classifier
Micrococcaceae 07702
Super Taxa
Gram-Positive Cocci; Eubacteria; Bacteria; Microorganisms
Organism Name
Staphylococcus aureus (species): pathogen
Taxa Notes
Bacteria, Eubacteria, Microorganisms

ORGANISM:
Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name

mouse (common): host, animal model
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
REGISTRY NUMBER: **129791-92-0 (rifalazil)**
13292-46-1 (rifampin)

L160 ANSWER 13 OF 21 USPATFULL on STN
ACCESSION NUMBER: 2005:143867 USPATFULL
TITLE: **Rifalazil** formulations
INVENTOR(S): **Michaelis, Arthur F.**, Devon, PA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005123602	A1	20050609
APPLICATION INFO.:	US 2004-950917	A1	20040927 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-506107P	20030925 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: CLARK & ELBING LLP, 101 FEDERAL STREET, BOSTON, MA, 02110, US
NUMBER OF CLAIMS: 28
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 1636
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention features pharmaceutical compositions including **rifalazil** and a micelle-forming excipient and methods of use thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI **Rifalazil** formulations
IN **Michaelis, Arthur F.**, Devon, PA, UNITED STATES
AB The invention features pharmaceutical compositions including **rifalazil** and a micelle-forming excipient and methods of use thereof.
SUMM **Rifalazil**, an ansamycin-class antibiotic, has been described in U.S. Pat. No. 4,983,602, where its antibacterial activity has been disclosed.
SUMM A microgranulated formulation of **rifalazil** is disclosed in U.S. Pat. No. 5,547,683. This microgranulated **rifalazil** was shown to exhibit improved oral bioavailability in comparison to **rifalazil** crystals, mortar-milled crystals, and suspensions of mortar-milled crystals as determined by the relative AUCs produced for each formulation orally administered to beagles. Phase I clinical trials for **rifalazil** are described in U.S. Pat. Nos. 6,566,354 and 6,316,433.
SUMM A formulation for the oral administration of **rifalazil** that produces more consistent pharmacokinetics and an enhanced degree of bioavailability among subjects is desirable.
SUMM We have discovered that the oral bioavailability of **rifalazil** may be increased to a surprising degree and the coefficient of variation in pharmacokinetic parameters (e.g., C.sub.max and AUC.sub.∞) may

be decreased to a surprising degree when **rifalazil** is formulated with a sufficient amount of a micelle-forming excipient.

SUMM Accordingly, in one aspect, the invention features a pharmaceutical composition for oral administration in unit dosage form including **rifalazil** and an amount of micelle-forming excipient sufficient to produce, upon administration to fasted patients, a coefficient of variation in C.sub.max. . .

SUMM The invention also features a pharmaceutical composition for oral administration in unit dosage form including **rifalazil** and an amount of micelle-forming excipient sufficient to produce, upon administration to fasted patients, a coefficient of variation in AUC.sub.128. . .

SUMM The invention features a pharmaceutical composition for oral administration in unit dosage form including **rifalazil** and an amount of micelle-forming excipient sufficient to produce, upon administration to fasted patients, a mean bioavailability of greater than. . .

SUMM . . . further features a pharmaceutical composition in the form of a liquid-filled capsule suitable for oral administration to a human containing **rifalazil** and one or more micelle-forming excipients

SUMM The liquid-filled capsule may include a hydrophilic polymer to promote the release of **rifalazil** after administration. Examples of hydrophilic polymers that can be used include, without limitation, polyoxyethylenes and hyaluronic acid. Desirably, the hydrophilic. . .

SUMM The liquid-filled capsule of **rifalazil** can include a gelling agent to promote viscosity. Desirably, the gelling agent is a polyoxyethylene-polyoxypropylene block copolymer. These gelling agents. . . ranging from 1000 to 15000 daltons, and with ethylene oxide/propylene oxide ratios between 0.1 and 0.8 by weight. Formulations of **rifalazil** according to the invention may include one or more of the polyoxyethylene-polyoxypropylene block copolymers above. Desirably, the gelling agent is. . .

SUMM The liquid-filled capsule of **rifalazil** can include water to prevent dehydration of the capsule. Desirably, the liquid-filled capsule of **rifalazil** includes between 0.5% and 10%, 0.5% and 8%, 0.5% and 7%, 0.5% and 6%, 0.5% and 5%, 1% and 7%,. . .

SUMM . . . acid esters, lower alcohol fatty acid esters, and ionic surfactants. Any micelle-forming excipient described herein may be used in the **rifalazil** formulations of the invention. Desirably, the liquid-filled capsule of **rifalazil** includes one or more micelle-forming excipients selected from sodium lauryl sulfate, polyoxyl-40 stearate, PEG-3 castor oil, PEG-5 castor oil, PEG-9. . .

SUMM . . . and 25, 0.1 and 20, 0.1 and 15, 0.1 and 10, 0.1 and 5, or 0.2 and 20 mg of **rifalazil.** Desirably, the pharmaceutical composition contains about 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 10, 12.5, 15, 20, 25, 30, 35, 40, 45, or 50 mg of **rifalazil.**

SUMM . . . of treating a bacterial infection in a patient. The method includes the step of administering a unit dosage form including **rifalazil** and an amount of micelle-forming excipient sufficient to produce, upon administration to fasted patients, a coefficient of variation in C.sub.max of less than 60%, wherein the **rifalazil** is administered in an amount effective to treat the infection. Desirably, the coefficient of variation in C.sub.max is less than. . .

SUMM . . . method of treating a bacterial infection in a patient that includes the step of administering a unit dosage form including **rifalazil** and an amount of micelle-forming excipient sufficient to produce, upon administration to fasted patients, a coefficient of variation in AUC.sub.∞ of less than 40%, wherein the

rifalazil is administered in an amount effective to treat the infection. Desirably, the coefficient of variation in AUC.sub.∞ is less than. . .

SUMM . . . method of treating a bacterial infection in a patient that includes the step of administering a unit dosage form including **rifalazil** and an amount of micelle-forming excipient sufficient to produce, upon administration to fasted patients, a mean bioavailability of greater than 30%, wherein the **rifalazil** is administered in an amount effective to treat the infection. Desirably, the mean bioavailability is greater than 35%, 40%, 45%,. . .

SUMM . . . a patient that includes the step of administering a unit dosage form in the form of a liquid-filled capsule including **rifalazil** and a micelle-forming excipient, wherein the **rifalazil** is administered in an amount effective to treat the infection.

SUMM . . . an infection by multi-drug resistant bacteria in a patient. The method includes administering to the patient a liquid-filled capsule including **rifalazil** and a micelle-forming excipient, or any other pharmaceutical composition of the invention, wherein the **rifalazil** is administered in an amount effective to treat the multi-drug resistant infection. Resistant strains of bacteria include penicillin-resistant, methicillin-resistant, quinolone-resistant,. . .

SUMM The invention also features a method of treating or preventing the development of an **atherosclerosis**-associated disease in a patient. The method includes administering to the patient a liquid-filled capsule including **rifalazil** and a micelle-forming excipient, or any other pharmaceutical composition of the invention, wherein the **rifalazil** is administered in an amount effective to treat or prevent the development of the **atherosclerosis**-associated disease in the patient. The patient is typically diagnosed as having the **atherosclerosis** -associated disease (or being at increased risk of developing the disease) or as having macrophages or foam cells infected with C. pneumoniae prior to the administration of a liquid-filled **rifalazil** capsule.

SUMM . . . of C-reactive protein in a patient in need thereof. This method includes administering to the patient a liquid-filled capsule including **rifalazil** and a micelle-forming excipient, or any other pharmaceutical composition of the invention, wherein the **rifalazil** is administered in an amount effective to reduce the level of C-reactive protein in the patient. In one embodiment, the. .

SUMM . . . or foam cells in a patient in need thereof. This method includes administering to the patient a liquid-filled capsule including **rifalazil** and a micelle-forming excipient, or any other pharmaceutical composition of the invention, wherein the **rifalazil** is administered in an amount effective to reduce C. pneumoniae replication in macrophages or foam cells in the patient.

SUMM . . . infection in macrophages or foam cells in a patient. The method includes administering to the patient a liquid-filled capsule including **rifalazil** and a micelle-forming excipient, or any other pharmaceutical composition of the invention, wherein the **rifalazil** is administered in an amount effective to treat the C. pneumoniae infection in macrophages or foam cells in the patient.

SUMM . . . with an infection of C. pneumoniae. This method includes the step of administering to the patient a liquid-filled capsule including **rifalazil** and a micelle-forming excipient, or any other pharmaceutical composition of the invention, wherein the **rifalazil** is administered in an amount effective to treat the infection.

SUMM . . . a bacterium having a multiplying form and a non-multiplying form by administering to the patient (i) a liquid-filled capsule including **rifalazil** and a micelle-forming excipient, or any other pharmaceutical composition of the invention, and (ii) a second antibiotic that is effective. . .

SUMM . . . take as long as a week. After this has been achieved, the patient is then administered a liquid-filled capsule including **rifalazil** and a micelle-forming excipient, wherein the **rifalazil** is administered in an amount and for a duration effective to complete the treatment of the patient. Antibiotics that are. . .

SUMM . . . capable of establishing a cryptic phase. The method includes the step of administering to the patient a liquid-filled capsule including **rifalazil** and a micelle-forming excipient, or any other pharmaceutical composition of the invention, wherein the **rifalazil** is administered in an amount effective to treat the patient.

SUMM . . . cryptic phase of a bacterial infection. This method includes the step of administering to the patient a liquid-filled capsule including **rifalazil** and a micelle-forming excipient, or any other pharmaceutical composition of the invention. The administering is for a time and in. . .

SUMM . . . to treat the multiplying form, and (b) treating the non-multiplying form of the bacteria by administering a liquid-filled capsule including **rifalazil** and a micelle-forming excipient, or any other pharmaceutical composition of the invention, wherein the administering is for a time and. . .

SUMM . . . disease or infection in the patient. The method includes the step of administering to the patient a liquid-filled capsule including **rifalazil** and a micelle-forming excipient, or any other pharmaceutical composition of the invention, wherein the **rifalazil** is administered in an amount effective to treat the infection. The method may be employed as an initial treatment of. . .

SUMM For any of the methods described herein, **rifalazil** may be administered in conjunction with one or more additional agents such as anti-inflammatory agents (e.g., non-steroidal anti-inflammatory drugs (NSAIDs;. . . be administered within 14 days, 7 days, 1 day, 12 hours, or 1 hour of the administration of a liquid-filled **rifalazil** capsule, or simultaneously therewith. The additional therapeutic agents may be present in the same or different pharmaceutical compositions as the liquid-filled **rifalazil** capsule. When present in different pharmaceutical compositions, different routes of administration may be used. For example, a second agent may be administered orally or by intramuscular or subcutaneous injection. Agents that can be administered in conjunction with **rifalazil** include any of the agents described herein.

SUMM In any of the above methods, **rifalazil** can be administered in a unit dosage form including **rifalazil** and a micelle-forming excipient. The micelle-forming excipient is present in an amount sufficient to produce, upon administration to fasted patients,. . .

SUMM The invention features a method of reducing the food effect exhibited by **rifalazil** administered to a patient. The method includes the steps of: (i) mixing **rifalazil** with a micelle-forming excipient; and (ii) administering the mixture of step (i) to the patient, wherein the mixture includes between. . .

SUMM The invention further features a method of increasing the oral bioavailability of **rifalazil** administered to a patient. The method includes the steps of: (i) mixing **rifalazil** with a micelle-forming excipient; and (ii) administering the mixture of step (i) to the patient, wherein the mixture includes 20%. . .

SUMM . . . "bioavailability" refers to the fraction of drug absorbed following oral administration to a patient. Under fasted conditions the bioavailability of **rifalazil** formulated as described herein is at least 25%, but may be greater than 30%, 35%, 40%, 45%, or even 50%.

SUMM By "C.sub.max" is meant the maximum concentration of **rifalazil** achieved in the blood after dosing.

SUMM By "AUC.sub.∞" is meant the integrated area under the **rifalazil** plasma concentration versus time curve from t=0 to ∞.

SUMM By "food effect" is meant a difference between mean pharmacokinetic parameters C.sub.max, T.sub.max, AUC.sub.∞, and bioavailability for **rifalazil** administered under fasted conditions in comparison to **rifalazil** administered under fed conditions.

SUMM . . . herein, "reducing the food effect" refers to narrowing the difference between any one of C.sub.max, T.sub.max, AUC.sub.∞, and bioavailability for **rifalazil** administered under fasted conditions in comparison to **rifalazil** administered under fed conditions, such that the differences are less than those observed for microgranulated **rifalazil.**

SUMM As used herein, the term "administration" or "administering" refers to peroral administration of **rifalazil** to a patient.

SUMM . . . in C.sub.max, decrease the coefficient of variation in AUC.sub.∞, reduce the food effect, or increase bioavailability in comparison to microgranulated **rifalazil.** The sufficient amount of micelle-forming excipient used to practice the invention varies depending upon the amount of **rifalazil** in the unit dosage formulation and the nature of the micelle-forming excipient. The sufficient amount can be determined by performing. . .

SUMM By "effective" amount is meant the amount of **rifalazil** required to treat or prevent an infection or a disease associated with an infection. The effective amount of **rifalazil** used to practice the invention for therapeutic or prophylactic treatment of conditions caused by or contributed to by a microbial. . .

SUMM . . . unitary dosages, such as a pill, tablet, caplet, hard capsule or soft capsule, each unit containing a predetermined quantity of **rifalazil.** The unit dosage forms of the invention include **rifalazil** and a micelle-forming excipient.

SUMM By "**atherosclerosis**" is meant the progressive accumulation of smooth muscle cells, immune cells (e.g., lymphocytes, macrophages, or monocytes), lipid products (e.g., lipoproteins, or cholesterol), cellular waste products, calcium, or other substances within the inner lining of an **artery**, resulting in the narrowing or obstruction of the blood vessel and the development of **atherosclerosis** -associated diseases. **Atherosclerosis** is typically manifested within large and medium-sized **arteries**, and is often characterized by a state of chronic inflammation within the **arteries.**

SUMM By "**atherosclerosis**-associated disease" is meant any disorder that is caused by or is associated with **atherosclerosis.** Typically, **atherosclerosis** of the coronary **arteries** commonly causes coronary **artery** disease, **myocardial** infarction, coronary thrombosis, and **angina** pectoris. **Atherosclerosis** of the **arteries** supplying the central nervous system frequently provokes **strokes** and transient **cerebral ischemia.** In the peripheral circulation, **atherosclerosis** causes intermittent **claudication** and **gangrene** and can jeopardize limb viability. **Atherosclerosis** of an **artery** of the splanchnic circulation can cause mesenteric **ischemia.**

Atherosclerosis can also affect the kidneys directly (e.g., renal **artery** stenosis).

SUMM A patient who is being treated for an **atherosclerosis**-associated disease is one who a medical practitioner has diagnosed as having such a disease. Diagnosis may be by any suitable means. Methods for diagnosing **atherosclerosis** by measuring systemic inflammatory markers are described, for example, in U.S. Pat. No. 6,040,147, hereby incorporated by reference. Diagnosis and monitoring may employ an **electrocardiogram**, chest X-ray, **echocardiogram**, **cardiac** catheterization, ultrasound (for the measurement of vessel wall thickness), or measurement of blood levels of CPK, CPK-MB, myoglobin, troponin, homocysteine, or C-reactive protein. A patient in whom the development of an **atherosclerosis**-associated disease is being prevented is one who has not received such a diagnosis. One in the art will understand that these patients may have been subjected to the same tests (**electrocardiogram**, chest X-ray, etc.) or may have been identified, without examination, as one at high risk due to the presence of. . . one or more risk factors (e.g., family history, hypertension, diabetes mellitus, high cholesterol levels). Thus, prophylactic administration of a liquid-filled **rifalazil** capsule is considered to be preventing the development of an **atherosclerosis**-associated disease.

SUMM An **atherosclerosis**-associated disease has been treated or prevented when one or more tests of the disease (e.g., any of those described above). . . improved or the patient's risk reduced. In one example, a reduction in C-reactive protein to normal levels indicates that an **atherosclerosis**-associated disease has been treated or prevented.

SUMM . . . of C. pneumoniae. Any suitable method may be employed (e.g., determination of C. pneumoniae in blood monocytes or in the **atheroma** itself (e.g., in macrophages or foam cells present in the fatty streak), or detection of C. pneumoniae DNA, RNA, or. . .

SUMM . . . These organisms cause diarrhea. Antibiotic-associated bacterial diarrhea includes such conditions as C. difficile associated diarrhea (CDAD) and pseudomembranous colitis. When **rifalazil** is administered as a liquid-filled capsule for the treatment of a C. difficile infection, an effective amount of **rifalazil** is the amount required to eradicate C. difficile from the patient, or the amount which prevents an infection of C.. . .

SUMM . . . mononuclear cells (e.g., macrophages, lymphocytes, and plasma cells), tissue destruction, and fibrosis. Non-limiting examples of inflammatory disease include asthma, coronary **artery** disease, arthritis, conjunctivitis, lymphogranuloma venerum, and salpingitis.

SUMM When administered to a human, **rifalazil** formulations described herein provide an increase in the bioavailability of **rifalazil** in comparison to the administration of microgranulated **rifalazil** disclosed in U.S. Pat. No. 5,547,683. The **rifalazil** formulations also decrease the coefficient of variation in pharmacokinetic parameters (e.g., C.sub.max and AUC.sub.∞) in comparison to the microgranulated formulation.

DRWD FIG. 1 is a graph depicting the dissolution rates of **rifalazil** from liquid-filled hard capsules in acidic media, simulated intestinal media, and water.

DRWD FIG. 2 is a graph depicting the dissolution rate of **rifalazil** from microgranular powder-filled hard capsules in acidic media.

DRWD FIG. 3 is a graph depicting the mean plasma **rifalazil** concentrations in dogs, fed or fasted, upon administration (PO) of liquid-filled capsules or microgranulated-filled capsules of **rifalazil.**

DETD The invention provides pharmaceutical formulations including

rifalazil and a micelle-forming excipient in an amount sufficient to alter the pharmacokinetics of **rifalazil**, e.g., by decreasing the coefficient of variation in C.sub.max, decreasing the coefficient of variation in AUC.sub.∞, reducing the food effect, and/or increasing the bioavailability of **rifalazil** in comparison to the microgranulated formulation of **rifalazil.**

DETD As described herein, micelle-forming excipients can be added to **rifalazil** in a unit dosage form for oral administration. The excipients likely promote the solubilization of **rifalazil** in the gut, enhancing absorption and enhancing the uniformity of the bioavailability of **rifalazil.** The excipients used are restricted to those that have a high degree of safety in humans.

DETD A variety of micelle-forming excipients may be used for the formulation of **rifalazil** including those disclosed in U.S. Pat. No. 6,365,637, incorporated herein by reference and compounds belonging to the following classes: polyethoxylated. . .

DETD Polyethoxylated fatty acids may be used as excipients for the formulation of **rifalazil.** Examples of commercially available polyethoxylated fatty acid monoester surfactants include: PEG 4-100 monolaurate (Crodet L series, Croda), PEG 4-100 monooleate. . . oleate (Albunol 200 MO, Taiwan Surf.), PEG-400 oleate (LACTOMUL, Henkel), and PEG-600 oleate (Albunol 600 MO, Taiwan Surf.). Formulations of **rifalazil** according to the invention may include one or more of the polyethoxylated fatty acids above.

DETD Polyethylene glycol fatty acid diesters may also be used as excipients for the formulation of **rifalazil.** Examples of commercially available polyethylene glycol fatty acid diesters include: PEG-4 dilaurate (Mapeg® 200 DL, PPG), PEG-4 dioleate (Mapeg® 200. . . (Kessco® PEG 1540 DS, Stepan), PEG-400 dioleate (Cithrol 4DO series, Croda), and PEG-400 distearate Cithrol 4DS series, Croda). Formulations of **rifalazil** according to the invention may include one or more of the polyethylene glycol fatty acid diesters above.

DETD PEG-fatty acid mono- and di-ester mixtures may be used as excipients for the formulation of **rifalazil.** Examples of commercially available PEG-fatty acid mono- and di-ester mixtures include: PEG 4-150 mono, dilaurate (Kessco® PEG 200-6000 mono, Dilaurate,. . . mono, dioleate (Kessco® PEG 200-6000 mono, Dioleate, Stepan), and PEG 4-150 mono, distearate (Kessco® 200-6000 mono, Distearate, Stepan). Formulations of **rifalazil** according to the invention may include one or more of the PEG-fatty acid mono- and di-ester mixtures above.

DETD In addition, polyethylene glycol glycerol fatty acid esters may be used as excipients for the formulation of **rifalazil.** Examples of commercially available polyethylene glycol glycerol fatty acid esters include: PEG-20 glyceryl laurate (Tagat® L, Goldschmidt), PEG-30 glyceryl laurate. . . and Aldo® MS-20 KFG, Lonza), PEG-20 glyceryl oleate (Tagat® O, Goldschmidt), and PEG-30 glyceryl oleate (Tagat® O2, Goldschmidt). Formulations of **rifalazil** according to the invention may include one or more of the polyethylene glycol glycerol fatty acid esters above.

DETD Alcohol-oil transesterification products may also be used as excipients for the formulation of **rifalazil.** Examples of commercially available alcohol-oil transesterification products include: PEG-3 castor oil (Nikkol CO-3, Nikko), PEG-5, 9, and 16 castor oil. . . Thus, derivatives of these vitamins, such as tocopheryl PEG-1000 succinate (TPGS, available from Eastman), are also suitable surfactants. Formulations of **rifalazil** according to the invention may include one or more of the alcohol-oil transesterification products above.

DETD Polyglycerized fatty acids may also be used as excipients for the formulation of **rifalazil**. Examples of commercially available polyglycerized fatty acids include: polyglyceryl-2 stearate (Nikkol DGMS, Nikko), polyglyceryl-2 oleate (Nikkol DGMO, Nikko), polyglyceryl-2 isostearate. . . Nikko), polyglyceryl-101 decaoleate (Drewpol 10-10-O, Stepan), polyglyceryl-10 mono, dioleate (Caprol® PGE 860, ABITEC), and polyglyceryl polyricinoleate (Polymuls, Henkel). Formulations of **rifalazil** according to the invention may include one or more of the polyglycerized fatty acids above.

DETD In addition, propylene glycol fatty acid esters may be used as excipients for the formulation of **rifalazil**. Examples of commercially available propylene glycol fatty acid esters include: propylene glycol monocaprylate (Capryol 90, Gattefosse), propylene glycol monolaurate (Lauroglycol. . . distearate (Kessco® PGDS, Stepan), propylene glycol dicaprylate (Nikkol Sefsol 228, Nikko), and propylene glycol dicaprate (Nikkol PDD, Nikko). Formulations of **rifalazil** according to the invention may include one or more of the propylene glycol fatty acid esters above.

DETD Mixtures of propylene glycol esters and glycerol esters may also be used as excipients for the formulation of **rifalazil**. One preferred mixture is composed of the oleic acid esters of propylene glycol and glycerol (Arlacel 186). Examples of these surfactants include: oleic (ATMOS 300, ARLACEL 186, ICI), and stearic (ATMOS 150). Formulations of **rifalazil** according to the invention may include one or more of the mixtures of propylene glycol esters and glycerol esters above.

DETD Furthermore, mono- and diglycerides may be used as excipients for the formulation of **rifalazil**. Examples of commercially available mono- and diglycerides include: monopalmitolein (C16:1) (Larodan), monoelaidin (C18:1) (Larodan), monocaproin (C6) (Larodan), monocaprylin (Larodan), monocaprin. . . (GELUCIRE 39/01, Gattefosse), dipalmitolein (C16:1) (Larodan), 1,2 and 1,3-diolein (C18:1) (Larodan), dielaidin (C18:1) (Larodan), and dilinolein (C18:2) (Larodan). Formulations of **rifalazil** according to the invention may include one or more of the mono- and diglycerides above.

DETD Sterol and sterol derivatives may also be used as excipients for the formulation of **rifalazil**. Examples of commercially available sterol and sterol derivatives include: cholesterol, sitosterol, lanosterol, PEG-24 cholesterol ether (Solulan C-24, Amerchol), PEG-30 cholestanol. . . BPS-5, Nikko), PEG-10 soyasterol (Nikkol BPS-10, Nikko), PEG-20 soyasterol (Nikkol BPS-20, Nikko), and PEG-30 soyasterol (Nikkol BPS-30, Nikko). Formulations of **rifalazil** according to the invention may include one or more of the sterol and sterol derivatives above.

DETD Polyethylene glycol sorbitan fatty acid esters may also be used as excipients for the formulation of **rifalazil**. Examples of commercially available polyethylene glycol sorbitan fatty acid esters include: PEG-10 sorbitan laurate (Liposorb L-10, Lipo Chem.), PEG-20 sorbitan. . . Pharma), polysorbate 40 (Tween® 40, Pharma), polysorbate 60 (Tween® 60, Pharma), and PEG-6 sorbitol hexastearate (Nikkol GS-6, Nikko). Formulations of **rifalazil** according to the invention may include one or more of the polyethylene glycol sorbitan fatty acid esters above.

DETD In addition, polyethylene glycol alkyl ethers may be used as excipients for the formulation of **rifalazil**. Examples of commercially available polyethylene glycol alkyl ethers include:. PEG-2 oleyl ether, oleth-2 (Brij 92/93, Atlas/ICI), PEG-3 oleyl ether, oleth-3. . . stearyl ether (Brij 76, ICI), PEG-20 stearyl ether (Brij 78, ICI), and PEG-100 stearyl ether (Brij 700, ICI). Formulations of **rifalazil** according to the invention may include one or more of the polyethylene

glycol alkyl ethers above.

DETD Sugar esters may also be used as excipients for the formulation of **rifalazil**. Examples of commercially available sugar esters include: sucrose distearate (SUCRO ESTER 7, Gattefosse), sucrose distearate/monostearate (SUCRO ESTER 11, Gattefosse), sucrose. . . monostearate (Crodesta F- 160, Croda), sucrose monopalmitate (SUCRO ESTER 15, Gattefosse), and sucrose monolaurate (Saccharose monolaurate 1695, Mitsubisbi-Kasei). Formulations of **rifalazil** according to the invention may include one or more of the sugar esters above.

DETD Polyethylene glycol alkyl phenols are also useful as excipients for the formulation of **rifalazil**. Examples of commercially available polyethylene glycol alkyl phenols include: PEG-10-100 nonylphenol series (Triton X series, Rohm & Haas) and PEG-15-100 octylphenol ether series (Triton N-series, Rohm & Haas). Formulations of **rifalazil** according to the invention may include one or more of the polyethylene glycol alkyl phenols above.

DETD Sorbitan fatty acid esters may also be used as excipients for the formulation of **rifalazil**. Examples of commercially sorbitan fatty acid esters include: sorbitan monolaurate (Span-20, Atlas/ICI), sorbitan monopalmitate (Span-40, Atlas/ICI), sorbitan monooleate (Span-80, Atlas/ICI),. . . sesquioleate (Arlacel-C, ICI), sorbitan tristearate (Span-65, Atlas/ICI), sorbitan monoisostearate (Crill 6, Croda), and sorbitan sesquistearate (Nikkol SS-15, Nikko). Formulations of **rifalazil** according to the invention may include one or more of the sorbitan fatty acid esters above.

DETD . . . IPM, Croda), isopropyl palmitate (Crodamol IPP, Croda), ethyl linoleate (Nikkol VF-E, Nikko), and isopropyl linoleate (Nikkol VF-IP, Nikko). Formulations of **rifalazil** according to the invention may include one or more of the lower alcohol fatty acid esters above.

DETD In addition, ionic surfactants may be used as excipients for the formulation of **rifalazil**. Examples of useful ionic surfactants include: sodium caproate, sodium caprylate, sodium caprate, sodium laurate, sodium myristate, sodium myristolate, sodium palmitate,. . . glyco cheno deoxycholate, sodium cholylsarcosinate, sodium N-methyl taurocholate, egg yolk phosphatides, hydrogenated soy lecithin, dimyristoyl lecithin, lecithin, hydroxylated lecithin, lysophosphatidylcholine, **cardiolipin**, sphingomyelin, phosphatidylcholine, phosphatidyl ethanolamine, phosphatidic acid, phosphatidyl glycerol, phosphatidyl serine, diethanolamine, phospholipids, polyoxyethylene-10 oleyl ether phosphate, esterification products of fatty. . . sodium salts, other cation counterions can also be used, such as, for example, alkali metal cations or ammonium. Formulations of **rifalazil** according to the invention may include one or more of the ionic surfactants above.

DETD . . . include any of the excipients described herein. The capsule will contain from, for example, 0.1 to about 100 mg of **rifalazil**. Liquid-filled capsules may, for example, contain either solutions or suspensions of **rifalazil**, depending upon the concentration of **rifalazil** within the capsule and the excipients used in the formulation.

DETD **Rifalazil** may be formulated as a pharmaceutically acceptable salt, such as a non-toxic acid addition salt or metal complexe that are. . .

DETD . . . ingredients, including, e.g., single or multiple unit capsule compositions, by varying the amount of hydrophilic polymer present in the liquid-filled **rifalazil** capsule, or by varying the amount of gelling agent in the formulated capsule.

DETD The **rifalazil** formulations described herein may also include a second therapeutic agent including, for example, another antibiotic, an anesthetic, an antimicrobial agent,. . .

DETD Antibiotics that can be admixed with the liquid-filled **rifalazil** capsule formulation include: aminoglycosides, such as amikacin, apramycin, arbekacin, bambermycins, butirosin, dibekacin, dihydrostreptomycin, fortimicin(s), fradiomycin, gentamicin, ispamicin, kanamycin, micronomicin, neomycin,. . .

DETD . . . of therapy (treatment or prophylaxis), the anticipated duration, and the severity of the infection or disease for which a liquid-filled **rifalazil** capsule is being administered. Additional considerations in dose selection include the type of infection, age of the patient (e.g., pediatric,. . . comorbidity. Determining what concentrations to employ are within the skills of the pharmacist, medicinal chemist, or medical practitioner formulating liquid-filled **rifalazil** capsule in combination with other therapeutic agents.

DETD . . . (MS), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), interstitial cystitis (IC), fibromyalgia (FM), autonomic nervous dysfunction (AND, neural-mediated hypotension); pyoderma **gangrenosum** (PG), chronic fatigue (CF), and chronic fatigue syndrome (CFS).

DETD . . . in immuno-compromised individuals by treating the non-multiplying form of the infection in an individual in need thereof, by administering a **rifalazil** formulation described herein, or such a **rifalazil** formulation in conjunction with an antibiotic effective against multiplying bacteria. Progress of the treatment can be evaluated, using the diagnostic. . .

DETD . . . bowel disease, ulcerative colitis, and Crohn's disease and vascular inflammatory pathologies, such as, but not limited to, disseminated intravascular coagulation, **atherosclerosis**, and Kawasaki's pathology are also suitable for treatment by methods described herein. The invention can also be used to treat inflammatory diseases such as coronary **artery** disease, hypertension, **stroke**, asthma, chronic hepatitis, multiple sclerosis, peripheral neuropathy, chronic or recurrent sore throat, laryngitis, tracheobronchitis, chronic vascular headaches (including migraines, cluster. . .

DETD Preparation of Liquid-Filled Capsules Containing 1 mg of **Rifalazil**

DETD PEG-35 castor oil (3,102 g), Pluronic® F68 (44 g), PEG 400 (1,034 g), water (220 g) and **rifalazil** (6.149 g) were mixed, resulting in a volume of 4.058 L and a **rifalazil** concentration of 0.66 mL/mg. Capsules (fill weight of 0.66 g and a fill volume of 0.68 mL) were filled with the liquid to produce liquid-filled capsules containing 1 mg of **rifalazil** each.

DETD Preparation of Liquid-Filled Capsules Containing 2.5 mg of **Rifalazil**

DETD PEG-35 castor oil (3,102 g), Pluronic® F68 (44 g), PEG 400 (1,034 g), water (220 g) and **rifalazil** (15.371 g) were mixed, resulting in a volume of 4.058 L and a **rifalazil** concentration of 0.264 mL/mg. Capsules (fill weight of 0.66 g and a fill volume of 0.68 mL) were filled with the liquid to produce liquid-filled capsules containing 2.5 mg of **rifalazil** each.

DETD Preparation of Liquid-Filled Capsules Containing 5 mg of **Rifalazil**

DETD PEG-35 castor oil (3,102 g), Pluronic® F68 (44 g), PEG 400 (1,034 g), water (220 g) and **rifalazil** (30.743 g) were mixed, resulting in a volume of 4.058 L and a **rifalazil** concentration of 0.132 mL/mg. Capsules (fill weight of 0.66 g and a fill volume of 0.68 mL) were filled with the liquid to produce liquid-filled capsules containing 5 mg of **rifalazil** each.

DETD Preparation of Liquid-Filled Capsules Containing 12.5 mg of

Rifalazil

DETD PEG-35 castor oil (3,740 g), Pluronic® F68 (44 g), PEG 400 (396 g), water (220 g) and **rifalazil** (77.519 g) were mixed, resulting in a volume of 4.093 L and a **rifalazil** concentration of 0.0528 mL/mg. Capsules (fill weight of 0.66 g and a fill volume of 0.68 mL) were filled with the liquid to produce liquid-filled capsules containing 12.5 mg of **rifalazil** each.

DETD The dissolution rates (mean of three measurements) of **rifalazil** in a liquid-filled capsule were monitored in different media: acidic media, simulated intestinal media, and water. The resulting data are. . . gelatin capsule due to the role of acid in the dissolution of gelatin. However, even in acidic media, which solubilizes **rifalazil**, the rate of release is much slower for **rifalazil** using a microgranular powder-filled hard gelatin capsule compared to the liquid filled capsules (compare FIGS. 1 and 2).

DETD Pharmacokinetic parameters were determined following a single peroral administration of 5 mg of **rifalazil** in healthy male beagle dogs. The **rifalazil** was formulated either as a liquid-filled capsule of Example 3 or as a powder-filled capsule containing microgranulated **rifalazil** as described in U.S. Pat. No. 5,547,683.

DETD Plasma samples (5.0 mL in EDTA tubes) for determination of **rifalazil** concentrations in plasma were obtained at hour: 0 (pre-dose) and at hours: 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0,. . . 36, 48, 72, 96, 168, 216 (Day 10), 336 (Day 15), 420, and 504 (Day 21), after administration of the **rifalazil** in either of the dosage forms. The mean plasma **rifalazil** concentrations in dogs, fed or fasted, upon administration (PO) of liquid-filled capsules or powder-filled capsules of **rifalazil** is shown in FIG. 3.

DETD . . . results are provided in Table 1. 100% bioavailability was determined by comparision to the pharmacokinetic profile observed for intravenously administered **rifalazil.**

TABLE 1

PK parameter	Micro-granulated fasted	Liquid-filled fasted	Micro-granulated fed	Liquid-filled fed
T.sub.max (h)	6.31 ± 7.11	1.87 ±. . .		

DETD The liquid-filled capsules of **rifalazil** exhibit a surprising increase in C.sub.max under both fed (1.8 fold increase) and fasted (3.5 fold increase) conditions and an increase in AUC.sub.∞ under both fed (1.7 fold increase) and fasted (2.0 fold increase) conditions in comparison to microgranulated **rifalazil.**

DETD The liquid-filled capsules of **rifalazil** also exhibit a surprising increase in bioavailability under both fed (1.7 fold increase) and fasted (2.0 fold increase) conditions in comparison to microgranulated **rifalazil.**

DETD . . . 1420) and C.sub.max (96.5 vs. 95.8), shows no change in PK behavior, e.g., no "food effect." In contrast, the microgranulated **rifalazil** exhibits a large food effect as demonstrated by the differences in AUC.sub.∞ (685 vs. 830) and C.sub.max (27.2 vs. 52.8). . .

DETD Changes in the formulation had no effect upon the elimination half-life (T.sub.1/2) of **rifalazil.**

CLM What is claimed is:

1. A pharmaceutical composition for oral administration in unit dosage form comprising **rifalazil** and an amount of micelle-forming excipient sufficient to produce, upon administration to fasted patients,

a coefficient of variation in C.sub.max. . .
2. A pharmaceutical composition for oral administration in unit dosage form comprising **rifalazil** and an amount of micelle-forming excipient sufficient to produce, upon administration to fasted patients, a coefficient of variation in AUC.sub.∞. . .
3. A pharmaceutical composition for oral administration in unit dosage form comprising **rifalazil** and an amount of micelle-forming excipient sufficient to produce, upon administration to fasted patients, a mean bioavailability of greater than. . .
4. A pharmaceutical composition in the form of a liquid-filled capsule, said capsule comprising **rifalazil** and a micelle-forming excipient.

15. The pharmaceutical composition of any of claims 1-4, said composition comprising between 0.1 and 100 mg of **rifalazil.**

16. The pharmaceutical composition of claim 15, said composition comprising between 0.1 and 25 mg of **rifalazil.**

18. A method of treating a bacterial infection in a patient, said method comprising administering to said patient a unit dosage form comprising **rifalazil** and an amount of micelle-forming excipient sufficient to produce, upon administration to fasted patients, a coefficient of variation in C.sub.max of less than 60%, wherein said **rifalazil** is administered in an amount effective to treat said infection.

. . . of treating a bacterial infection in a patient, said method comprising administering to said patient a unit dosage form comprising **rifalazil** and an amount of micelle-forming excipient sufficient to produce, upon administration to fasted patients, a coefficient of variation in AUC.sub.∞ of less than 40%, wherein said **rifalazil** is administered in an amount effective to treat said infection.

. . . of treating a bacterial infection in a patient, said method comprising administering to said patient a unit dosage form comprising **rifalazil** and an amount of micelle-forming excipient sufficient to produce, upon administration to fasted patients, a mean bioavailability of greater than 30%, wherein said **rifalazil** is administered in an amount effective to treat said infection.

. . . patient, said method comprising administering to said patient a unit dosage form in the form of a liquid-filled capsule comprising **rifalazil** and a micelle-forming excipient, wherein said **rifalazil** is administered in an amount effective to treat said infection.

23. The method of any of claims 18-21, wherein said **rifalazil** is administered for prophylaxis against an infection resulting from a surgical procedure or implantation of a prosthetic device.

. . . an infection by multi-drug resistant bacteria in a patient, said method comprising administering to said patient a liquid-filled capsule comprising **rifalazil** and a micelle-forming excipient, wherein said **rifalazil** is administered in an amount effective to treat said infection.

. . . replication in macrophages or foam cells in a patient, said method comprising administering to said patient a liquid-filled capsule comprising **rifalazil** and a micelle-forming excipient, wherein

said **rifalazil** is administered in an amount effective to reduce Chlamydia pneumoniae replication in macrophages or foam cells in said patient.

27. A method of reducing the food effect exhibited by **rifalazil** administered to a patient, said method comprising: (i) mixing **rifalazil** with a micelle-forming excipient; and (ii) administering the mixture of step (i) to said patient, wherein said mixture comprises between. . .

28. A method of increasing the oral bioavailability of **rifalazil** administered to a patient, said method comprising: (i) mixing **rifalazil** with a micelle-forming excipient; and (ii) administering the mixture of step (i) to said patient, wherein said mixture comprises between. . .

IT **129791-92-0**, Rifalazil
(oral formulations containing rifalazil in micelle-forming excipients)

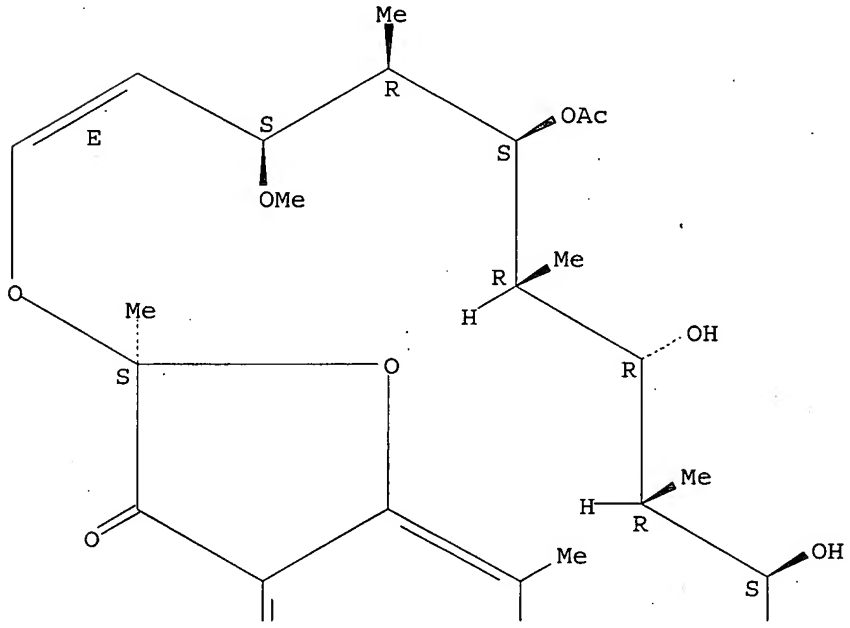
IT **129791-92-0**, Rifalazil
(oral formulations containing rifalazil in micelle-forming excipients)

RN 129791-92-0 USPATFULL

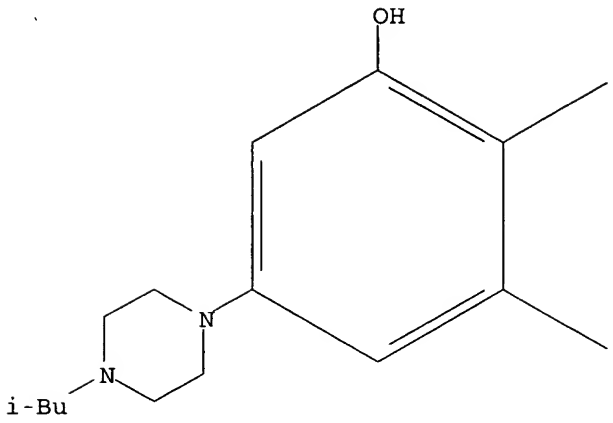
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

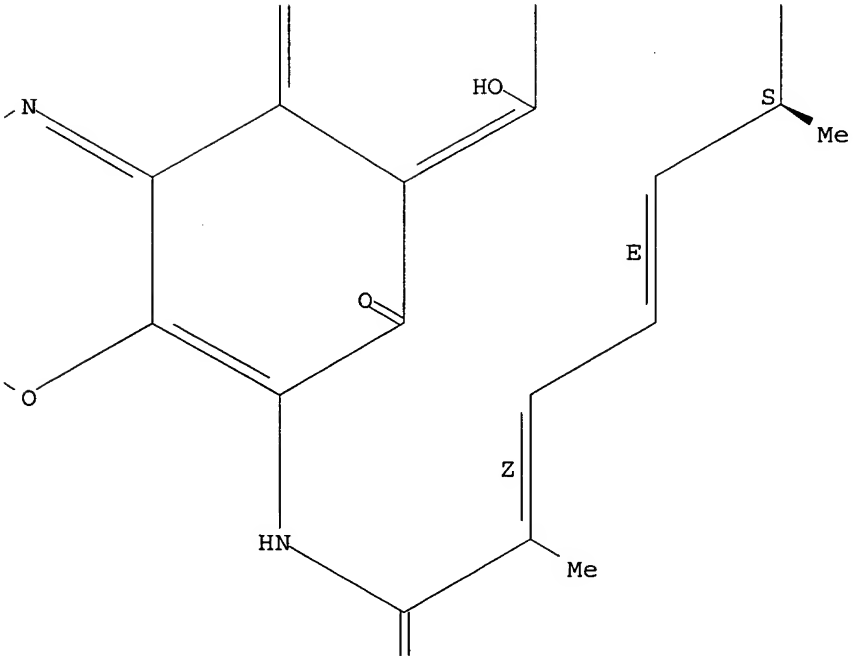
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

O

L160 ANSWER 14 OF 21 USPATFULL on STN
ACCESSION NUMBER: 2004:228018 USPATFULL
TITLE: Methods and reagents for treating or preventing **atherosclerosis** and diseases associated

therewith
INVENTOR(S): **Sayada, Chalom B.**, Luxembourg City, LUXEMBOURG

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004176404	A1	20040909
APPLICATION INFO.:	US 2003-735344	A1	20031211 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-433379P	20021212 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: CLARK & ELBING LLP, 101 FEDERAL STREET, BOSTON, MA, 02110
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1
LINE COUNT: 326
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention features a method for treating, preventing, or reducing the development of an **atherosclerosis**-associated disease in a patient by administering to the patient a rifamycin in an amount effective to treat, prevent, or prevent the development of the **atherosclerosis**-associated disease in the patient.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Methods and reagents for treating or preventing **atherosclerosis** and diseases associated therewith

IN **Sayada, Chalom B.**, Luxembourg City, LUXEMBOURG

AB The invention features a method for treating, preventing, or reducing the development of an **atherosclerosis**-associated disease in a patient by administering to the patient a rifamycin in an amount effective to treat, prevent, or prevent the development of the **atherosclerosis**-associated disease in the patient.

SUMM [0003] **Atheroclerosis**-associated diseases are the largest single cause of premature death in the western world. Although predisposition to **atherosclerosis** has traditionally been associated with age, social, and economic factors, a growing body of evidence has recently implicated various bacteria. . . . is Chlamydia (C.) pneumoniae, a pathogen involved in acute and chronic respiratory infections. On the basis of its presence in **atherosclerotic** lesions and its absence in healthy **artery** tissues, C. pneumoniae has been implicated in the initiation and pathogenesis of **atherosclerosis.** It has been suggested that C. pneumoniae lodges in the walls of blood vessels remaining there for years. The chronic inflammation triggered by the persistent bacterial infection within the **arterial** walls may induce host macrophages to remove fat, cholesterol, and other deposits from the vessel walls, ultimately causing **arterial** irritation and scarring. The consequent build-up in **arterial** plaques can foster blood clots and impede circulation, thus increasing susceptibility to a number of disorders, including **heart** attacks and **strokes.**

SUMM [0004] While the administration of antibiotics has been suggested to treat or prevent **atherosclerosis**-associated diseases by eradicating C. pneumoniae infection in **arteries**, little success has been reported. Thus, there is a need for improved methods for treating or preventing the development of **atherosclerosis** in patients infected with C. pneumoniae.

SUMM . . . that rifamycins are uniquely capable of reaching and

eradicating C. pneumoniae present in foam cells or macrophages found in the **arterial** fatty streaks that are associated with **atherosclerosis.**

SUMM [0006] Accordingly, the invention features a method of treating, reducing, or preventing the development of an **atherosclerosis** -associated disease in a patient by administering to the patient a rifamycin in an amount effective to treat, reduce, or prevent the development of the **atherosclerosis**-associated disease in the patient. Prior to the administration of the rifamycin, the patient may be diagnosed as having the **atherosclerosis**-associated disease (or being at increased risk of developing such disease) or as having macrophages or foam cells infected with C.. . .

SUMM . . . the rifamycin of the invention. When present in different pharmaceutical compositions, different routes of administration may be used. For example, **rifalazil** may be administered orally, while a second agent may be administered by intravenous, intramuscular, or subcutaneous injection.

SUMM [0013] By "**atherosclerosis**" is meant the progressive accumulation of smooth muscle cells, immune cells (e.g., lymphocytes, macrophages, or monocytes), lipid products (e.g., lipoproteins, or cholesterol), cellular waste products, calcium, or other substances within the inner lining of an **artery**, resulting in the narrowing or obstruction of the blood vessel and the development of **atherosclerosis**-associated diseases. **Atherosclerosis** is typically manifested within large and medium-sized **arteries** , and is often characterized by a state of chronic inflammation within the **arteries.**

SUMM [0014] By "**atherosclerosis**-associated disease" is meant any disorder that is caused by or is associated with **atherosclerosis** . Typically, **atherosclerosis** of the coronary **arteries** commonly causes coronary **artery** disease, **myocardial** infarction, coronary thrombosis, and **angina** pectoris. **Atherosclerosis** of the **arteries** supplying the central nervous system frequently provokes **strokes** and transient **cerebral ischemia.** In the peripheral circulation, **atherosclerosis** causes intermittent **claudication** and **gangrene** and can jeopardize limb viability. **Atherosclerosis** of an **artery** of the splanchnic circulation can cause mesenteric **ischemia.** **Atherosclerosis** can also affect the kidneys directly (e.g., renal **artery** stenosis).

SUMM [0015] A patient who is being treated for an **atherosclerosis** -associated disease is one who a medical practitioner has diagnosed as having such a disease. Diagnosis may be done by any suitable means. Methods for diagnosing **atherosclerosis** by measuring systemic inflammatory markers are described, for example, in U.S. Pat. No. 6,040,147, hereby incorporated by reference. Diagnosis and monitoring may employ an **electrocardiogram**, chest X-ray, **echocardiogram**, **cardiac** catheterization, ultrasound (for the measurement of vessel wall thickness), or measurement of blood levels of CPK, CPK-MB, myoglobin, troponin, homocysteine, or C-reactive protein. A patient in whom the development of an **atherosclerosis** -associated disease is being prevented is one who has not received such a diagnosis. One in the art will understand that these patients may have been subjected to the same tests (**electrocardiogram**, chest X-ray, etc.) or may have been identified, without examination, as one at high risk due to the presence of. . . diabetes mellitus, high cholesterol levels). Thus, prophylactic administration of a rifamycin is considered to be preventing the development of an **atherosclerosis**-associated disease.

SUMM [0016] An **atherosclerosis**-associated disease has been treated or prevented when one or more tests of the disease (e.g., any of the those described. . . improved or the patient's risk reduced. In one example, a reduction in C-reactive protein to normal levels indicates that an **atherosclerosis**-associated disease has been treated or prevented.

SUMM . . . of C. pneumoniae. Any suitable method may be employed (e.g., determination of C. pneumoniae in blood monocytes or in the **atheroma** itself (e.g., in macrophages or foam cells present in the fatty streak), or detection of C. pneumoniae DNA, C. pneumoniae. .

SUMM . . . a stent coated with a rifamycin. The stent can be, e.g., a wire mesh tube used to hold open an **artery.** Stents are typically inserted following angioplasty.

SUMM [0019] Rifamycins are compounds characterized by a chromophoric naphthohydroquinone group spanned by an aliphatic bridge. Exemplary rifamycins are **rifalazil** (3'-hydroxy-5'-(4-isobutyl-1-piperazinyl) benzoxazinorifamycin; also known as **KRM-1648**), rifampin, rifabutin, rifapentin, and rifaximin. Other rifamycins are disclosed in U.S. Pat. Nos. 4,690,919; 4,983,602; 5,786,349; 5,981,522; 6,316,433 and 4,859,661,. . .

DETD [0020] We have discovered that administration of a rifamycin is effective to treat, reduce, or prevent the development of an **atherosclerosis**-associated disease in a patient.

DETD . . . to the present invention, a rifamycin may be administered by any route that results in an effective amount reaching the **atheroma** or the foam cells (lipid-laden macrophages that constitute the fatty streak). The rifamycin is normally administered in an amount ranging. . .

DETD [0022] Rifamycins include **rifalazil**, rifampin, rifabutin, rifapentin, rifaximin, and compounds described by formula I: ##STR1##

CLM What is claimed is:

1. A method of treating, preventing, or reducing the development of an **atherosclerosis**-associated disease in a patient in need thereof, said method comprising administering to said patient a rifamycin in an amount effective to treat, prevent, or reduce the development of said **atherosclerosis**-associated disease in said patient.

14. The method of claim 1, wherein said **atherosclerosis** -associated disease is coronary **artery** disease, **myocardial** infarction, **angina** pectoris, **stroke** , **cerebral ischemia**, intermittent **claudication**, **gangrene**, mesenteric **ischemia**, temporal **arteritis**, or renal **artery** stenosis.

. . . 15. The method of claim 1, wherein, prior to administration of said rifamycin, said patient is diagnosed as having said **atherosclerosis**-associated disease.

L160 ANSWER 15 OF 21 USPATFULL on STN
ACCESSION NUMBER: 2004:203948 USPATFULL
TITLE: **Rifalazil** compositions and therapeutic regimens
INVENTOR(S): **Cabana, Bernard E.**, Montgomery Village, MD, UNITED STATES
Michaelis, Arthur F., Devon, PA, UNITED STATES
Magnant, Gary P., Topsfield, MA, UNITED STATES

Sayada, Chalom B., Luxembourg City, LUXEMBOURG

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004157840	A1	20040812
APPLICATION INFO.:	US 2003-668792	A1	20030923 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-412958P	20020923 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: CLARK & ELBING LLP, 101 FEDERAL STREET, BOSTON, MA, 02110
NUMBER OF CLAIMS: 51
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Page(s)
LINE COUNT: 1369
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention features low-dosage **rifalazil** compositions and therapeutic regimens which are useful for the treatment of bacterial infections.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI **Rifalazil** compositions and therapeutic regimens

IN **Cabana, Bernard E.**, Montgomery Village, MD, UNITED STATES
IN **Michaelis, Arthur F.**, Devon, PA, UNITED STATES
IN **Magnant, Gary P.**, Topsfield, MA, UNITED STATES
IN **Sayada, Chalom B.**, Luxembourg City, LUXEMBOURG

AB The invention features low-dosage **rifalazil** compositions and therapeutic regimens which are useful for the treatment of bacterial infections.

SUMM [0003] **Rifalazil**, an ansamycin-class antibiotic, has been described in the U.S. Pat. No. 4,983,602, where its antibacterial activity has been disclosed. Dosages. . . when clinical trials with these doses of the antibiotic were administered daily, many adverse reactions occurred and the treatment with **rifalazil** was discontinued.

SUMM [0004] More recently, a once or twice-a-week dosing regimen for **rifalazil** was found to be efficacious against mycobacterium species, as described in U.S. Pat. No. 6,316,433. This regimen included doses ranging from 1 to 100 mg of **rifalazil** once or twice weekly. This dosing regimen reduced, but did not eliminate, the incidence of adverse reactions, which include the. . .

SUMM [0005] We have discovered that, when administered at low doses, **rifalazil** resides in tissues an unexpectedly long time. As a result, therapeutically useful concentrations of **rifalazil** can be obtained by administering a low-dosage regimen. Such regimens may reduce the risk of adverse reactions.

SUMM [0006] In one aspect, the invention features a pharmaceutical composition containing a unit dosage form of **rifalazil** in an amount between 0.01 and 5 mg. Desirably, the unit dosage form contains between 0.1 and 5, 0.1 and. . . and 0.8, 0.2 and 0.7, 0.01 and 4.8, 0.01 and 4, 0.01 and 3, or 0.05 and 4.8 mg of **rifalazil.** The unit dosage form can be a tablet, pill, capsule, or caplet, among others.

SUMM [0008] The invention also features a method of treating a bacterial infection by administering a low-dosage **rifalazil** regimen. The low-dosage regimen includes the step of administering to a patient

between 0.01 and 10 mg of **rifalazil** over a period of four to fourteen days. Desirably, between 0.1 and 10, 0.01 and 8, 0.01 and 6, 0.05. . . and 6, 0.1 and 5, 0.1 and 4, 0.1 and 3, 0.1 and 2.6, or 0.2 and 2.0 mg of **rifalazil** is administered over a period of five to ten days, or over a period of seven days.

SUMM [0009] The invention also features a method of treating a bacterial infection by administering **rifalazil** daily. This method includes the step of administering to a patient between 0.01 and 5 mg of **rifalazil** daily over a period of at least 2 days. Desirably, between 0.1 and 5, 0.1 and 4, 0.1 and 3,. . . and 2.6, 0.1 and 1.8, 0.01 and 4, 0.05 and 4.6, 0.05 and 4, or 0.1 and 1.6 mg of **rifalazil** is administered daily for a period of at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20,. . .

SUMM [0010] The invention further features a method of treating a bacterial infection by administering **rifalazil** in a loading-dose regimen. The loading-dose regimen can include: (i) an initial administration of **rifalazil** at an average daily dose for 4 to 14 days, followed by less than half this average daily dose for the subsequent following 4 to 14 days; (ii) an average initial daily dose of **rifalazil** which is at least 200% of the average daily dose over two, three, four, or five subsequent dosing days; or (iii) administering **rifalazil** at a dose administered on Day 1 that is at least 200% of the dose administered on any of the. . .

SUMM . . . and 30, 4.5 and 20, 4.5 and 15, 5 and 14, 5 and 12, or 5 and 10 mg/day of **rifalazil.** Following the initial daily dose, maintenance doses of **rifalazil** are given to the patient to sustain a desired tissue concentration of **rifalazil** in the patient. The maintenance doses are greater than 0.01 mg of **rifalazil** per week. The maintenance doses can be administered as a low-dosage or daily regimen described herein.

SUMM . . . method includes the step of administering to the patient (i) a unit dosage form, low-dosage regimen, or loading-dose regimen of **rifalazil** described herein, and (ii) a second antibiotic that is effective against the multiplying form of the bacterium, wherein the two. . .

SUMM . . . After this has been achieved, the patient is then administered a unit dosage form, low-dosage regimen, or loading-dose regimen of **rifalazil** described herein in an amount and for a duration effective to complete the treatment of the patient. Antibiotics that are. . .

SUMM . . . a cryptic phase. The method includes the step of administering a unit dosage form, low-dosage regimen, or loading-dose regimen of **rifalazil** described herein to the patient.

SUMM . . . a bacterial infection. This method includes the step of administering a unit dosage form, low-dosage regimen, or loading-dose regimen of **rifalazil** described herein to a patient. The administering is for a time and in an amount effective to treat the cryptic. . .

SUMM . . . (b) treating the non-multiplying form of the bacteria by administering a unit dosage form, low-dosage regimen, or loading-dose regimen of **rifalazil** described herein to the patient, wherein the administering is for a time and in an amount effective to treat the. . .

SUMM [0022] The invention features a method for treating or preventing the development of an **atherosclerosis**-associated disease in a human patient. The method includes administering a unit dosage form, low-dosage regimen, or loading-dose regimen of **rifalazil** described herein to the patient, wherein the administering is for a time and in an amount effective to treat or prevent the development of the **atherosclerosis**-associated disease in the patient. The patient

is typically diagnosed as having the **atherosclerosis** -associated disease (or being at increased risk of developing the disease) or as having macrophages or foam cells infected with C. pneumoniae prior to a low-dosage administration of **rifalazil.**

SUMM . . . a human patient in need thereof. This method includes administering a unit dosage form, low-dosage regimen, or loading-dose regimen of **rifalazil** described herein to the patient, wherein the administering is for a time and in an amount effective to reduce the. . .

SUMM . . . a human patient in need thereof. This method includes administering a unit dosage form, low-dosage regimen, or loading-dose regimen of **rifalazil** described herein to the patient, wherein the administering is for a time and in an amount effective to reduce C.. . .

SUMM . . . foam cells in a human patient. The method includes administering a unit dosage form, low-dosage regimen, or loading-dose regimen of **rifalazil** described herein to the patient, wherein the administering is for a time and in an amount effective to treat the. . .

SUMM . . . with an infection of C. pneumoniae. The method includes administering a unit dosage form, low-dosage regimen, or loading-dose regimen of **rifalazil** described herein to the patient, wherein the administering is for a time and in an amount effective to treat the. . .

SUMM . . . disease or infection in the patient. The method includes administering a unit dosage form, low-dosage regimen, or loading-dose regimen of **rifalazil** described herein to the patient, wherein the administering is for a time and in an amount effective to treat the. . .

SUMM [0028] For any of the methods described herein, **rifalazil** may be administered in conjunction with one or more additional agents such as anti-inflammatory agents (e.g., non-steroidal anti-inflammatory drugs (NSAIDs;. . . may be administered within 14 days, 7 days, 1 day, 12 hours, or 1 hour of the low-dosage administration of **rifalazil** , or simultaneously therewith. The additional therapeutic agents may be present in the same or different pharmaceutical compositions as the formulation of **rifalazil.** When present in different pharmaceutical compositions, different routes of administration may be used. For example, a second agent may be administered orally or by intramuscular or subcutaneous injection. Agents that can be administered in conjunction with **rifalazil** include any of the agents described herein.

SUMM . . . an infection of C. trachomatis. The method includes the step of administering to the patient a single oral dose of **rifalazil.** Sexually transmitted diseases caused by C. trachomatis include, without limitation, urethritis, cervicitis, salpingitis, endometritis, epididymitis, lymphogranuloma venereum, proctitis, perihepatitis, and trachoma. The single oral dose of **rifalazil** is between 0.01 and 100 mg of **rifalazil.** Desirably, between 0.01 and 50, 0.01 and 25, 0.01 and 10, 0.01 and 5, 0.1 and 25, 0.1 and 10, 0.5 and 15, or 5 and 25 mg of **rifalazil** is administered in a single oral dose. The method also includes administering a unit dosage form of **rifalazil** described herein. Accordingly, between 0.01 and 5, 0.1 and 5, 0.1 and 4, 0.1 and 3, 0.1 and 2.5, 0.25. . . and 5, 1 and 4, 1 and 3, 0.5 and 4, 0.5 and 3, or 0.5 and 2 mg of **rifalazil** is administered as a single oral dose to treat the disease or infection caused by C. trachomatis.

SUMM [0030] The invention further features a pharmaceutical formulation including **rifalazil.** The formulation is packaged with a label or package insert providing instructions for the use of the formulation

wherein the instructions describe administration of **rifalazil** in a loading-dose regimen.

SUMM [0031] The pharmaceutical formulation may be a prepackaged therapeutic regimen including a first dosage unit which includes **rifalazil** ; a second dosage unit which includes a smaller dose of **rifalazil** than the first dosage unit; instructions for the administration of the first dosage unit prior to the second dosage unit;. . .

SUMM [0032] The dosage units may include one or more tablets, pills, capsules, or caplets. Desirably, the second dosage unit contains **rifalazil** in an amount between 0.01 and 5 mg per unit. Desirably, the second dosage unit contains **rifalazil** in an amount between 0.1 and 5, 0.1 and 4, 0.1 and 3, 0.1 and 2.5, 0.25 and 5, 0.25. . .

SUMM . . . forms" refers to physically discrete units suitable as unitary dosages for human subjects, each unit containing a predetermined quantity of **rifalazil** in amounts of less than 5 milligrams but sufficient to produce the desired therapeutic effect, in association with a suitable. . .

SUMM [0036] By "low-dosage regimen" is meant a regimen for the administration of **rifalazil** to a patient, wherein between 0.01 and 10 mg of **rifalazil** is administered over a period of four to fourteen days.

SUMM . . . and 6, 0.1 and 5, 0.1 and 4, 0.1 and 3, 0.1 and 2.6, or 0.2 and 2 mg of **rifalazil** administered over a period of five to ten days, or over a period of seven days.

SUMM [0038] By "loading-dose regimen" is meant a regimen for the administration of **rifalazil** that includes at least two administrations of **rifalazil** in which any of the following criteria are met: i) the average daily dose administered from the first day of. . .

SUMM [0040] By "average daily dose" is meant the administered dose, in milligrams, of **rifalazil** per unit time. The average daily dose is calculated from the instructed regimen. For example, 25 mg twice weekly is. . .

SUMM [0041] By "average initial daily dose" is meant the dose of **rifalazil** administered on Day 1 divided by the time until the next administration. For example, a dosing regimen that calls for administration of 10 mg of **rifalazil** on Day 1, followed by 2.5 mg on days 8, 10, 14, and 18, has an average initial daily dose. . .

SUMM [0042] By "average daily dose over N subsequent dosing days" is meant the sum of **rifalazil** administered in N dosing days subsequent to the day of the initial administration divided by the time over which N+1. . . subsequent to the initial administration are made. For example, a dosing regimen that calls for administration of 10 mg of **rifalazil** on Day 1, followed by 2.5 mg on days 8, 10, 14, 18, 23, and 27, has an average daily. . .

SUMM [0043] By "initial administration" is meant administration of **rifalazil** to a patient to whom **rifalazil** has not been administered in the previous 15 days. Desirably, the **rifalazil** has not been administered in the previous 22 days, 1 month, 2 months, or 3 months.

SUMM [0044] By "dose administered on Day 1" is meant the sum total of all **rifalazil** administered over the first 24 hours of the initial administration:

SUMM [0045] By "dosing day" is meant a day on which a **rifalazil** is administered to a patient to whom **rifalazil** has not been administered in the previous 24 hours, wherein the dose administered on a dosing day is the sum total of all **rifalazil** administered over a 24 hour period beginning from the first administration on this

day.

SUMM [0048] By "effective" amount is meant the amount of **rifalazil** required to treat or prevent an infection or a disease associated with an infection. The effective amount of **rifalazil** used to practice the invention for therapeutic or prophylactic treatment of conditions caused by or contributed to by a microbial. . .

SUMM [0050] By "**atherosclerosis**" is meant the progressive accumulation of smooth muscle cells, immune cells (e.g., lymphocytes, macrophages, or monocytes), lipid products (e.g., lipoproteins, or cholesterol), cellular waste products, calcium, or other substances within the inner lining of an **artery**, resulting in the narrowing or obstruction of the blood vessel and the development of **atherosclerosis**-associated diseases. **Atherosclerosis** is typically manifested within large and medium-sized **arteries**, and is often characterized by a state of chronic inflammation within the **arteries.**

SUMM [0051] By "**atherosclerosis**-associated disease" is meant any disorder that is caused by or is associated with **atherosclerosis**. Typically, **atherosclerosis** of the coronary **arteries** commonly causes coronary **artery** disease, **myocardial** infarction, coronary thrombosis, and **angina** pectoris. **Atherosclerosis** of the **arteries** supplying the central nervous system frequently provokes **strokes** and transient **cerebral ischemia.** In the peripheral circulation, **atherosclerosis** causes intermittent **claudication** and **gangrene** and can jeopardize limb viability. **Atherosclerosis** of an **artery** of the splanchnic circulation can cause mesenteric **ischemia.** **Atherosclerosis** can also affect the kidneys directly (e.g., renal **artery** stenosis).

SUMM [0052] A human patient who is being treated for an **atherosclerosis**-associated disease is one who a medical practitioner has diagnosed as having such a disease. Diagnosis may be by any suitable means. Methods for diagnosing **atherosclerosis** by measuring systemic inflammatory markers are described, for example, in U.S. Pat. No. 6,040,147, incorporated herein by reference. Diagnosis and monitoring may employ an **electrocardiogram**, chest X-ray, **echocardiogram**, **cardiac** catheterization, ultrasound (for the measurement of vessel wall thickness), or measurement of blood levels of CPK, CPK-MB, myoglobin, troponin, homocysteine, or C-reactive protein. A patient in whom the development of an **atherosclerosis**-associated disease is being prevented is one who has not received such a diagnosis. One in the art will understand that these patients may have been subjected to the same tests (**electrocardiogram**, chest X-ray, etc.) or may have been identified, without examination, as one at high risk due to the presence of one or more risk factors (e.g., family history, hypertension, diabetes mellitus, high cholesterol levels). Thus, prophylactic low-dosage administration of **rifalazil** is considered to be preventing the development of an **atherosclerosis**-associated disease.

SUMM [0053] An **atherosclerosis**-associated disease has been treated or prevented when one or more tests of the disease (e.g., any of the those described. . . improved or the patient's risk reduced. In one example, a reduction in C-reactive protein to normal levels indicates that an **atherosclerosis**-associated disease has been treated or prevented.

SUMM . . . of C. pneumoniae. Any suitable method may be employed (e.g., determination of C. pneumoniae in blood monocytes or in the **atheroma** itself (e.g., in macrophages or foam cells present in the fatty streak), or detection of C. pneumoniae DNA, RNA, or. . .

SUMM . . . These organisms cause diarrhea. Antibiotic-associated bacterial diarrhea includes such conditions as C. difficile associated diarrhea (CDAD) and pseudomembranous colitis. When **rifalazil** is administered at a low dosage for the treatment of a C. difficile infection, an effective amount of **rifalazil** is the amount required to eradicate C. difficile from the patient, or the amount which prevents an infection of C.. . .

SUMM . . . mononuclear cells (e.g., macrophages, lymphocytes, and plasma cells), tissue destruction, and fibrosis. Non-limiting examples of inflammatory disease include asthma, coronary **artery** disease, arthritis, conjunctivitis, lymphogranuloma venerum, and salpingitis.

SUMM [0071] While the invention is described herein in terms of **rifalazil**, the invention applies as well to **rifalazil** analogs. Analogs of **rifalazil** are compounds that satisfy formula (I): ##STR1##

SUMM . . . having 1 to 3 carbon atoms expressed by X.sup.3 is selected from methoxy, ethoxy, propoxy, isopropoxy, and cyclopropoxy. Analogs of **rifalazil** include those compounds disclosed in U.S. Pat. Nos. 4,690,919, 4,859,661, 4,983,602, 5,786,349, and 5,981,522, each of which is incorporated herein. . .

DRWD [0084] FIG. 1A is a graph depicting the observed plasma concentration of **rifalazil** in male subjects following the oral administration of a 2.5 mg dose of **rifalazil.**

DRWD [0085] FIG. 1B is a log-graph depicting the observed plasma concentration of **rifalazil** in male subjects following the oral administration of a 2.5 mg dose and the point at which the plasma concentration. . .

DRWD [0086] FIG. 2 is a diagram depicting a pharmacokinetic model for the absorption, distribution, and excretion of **rifalazil.**

DRWD [0087] FIG. 3 is a log-graph depicting the simulated **rifalazil** concentrations in plasma and tissue following a single 2.5 mg oral administration of **rifalazil** relative to the MIC for C. trachomatis.

DRWD [0088] FIG. 4 is a log-graph depicting the simulated **rifalazil** concentrations in plasma and tissue following a single 1.0 mg oral administration of **rifalazil** relative to the MIC for C. trachomatis.

DRWD [0089] FIG. 5 is a graph depicting the simulated **rifalazil** concentrations in plasma and tissue following a single 0.25 mg oral administration of **rifalazil** relative to the MIC for C. trachomatis.

DRWD [0090] FIG. 6 is a log-graph depicting the simulated **rifalazil** concentrations in plasma and tissue following five daily 1.0 mg oral administrations of **rifalazil** relative to the MIC for C. trachomatis.

DRWD [0091] FIG. 7 is a log-graph depicting the simulated **rifalazil** concentrations in plasma and tissue following five daily 0.25 mg oral administrations of **rifalazil** relative to the MIC for C. trachomatis.

DETD [0092] The invention provides **rifalazil** compositions and therapeutic regimens which are useful for the treatment of bacterial infections.

DETD [0093] The therapeutic regimen can be a low-dosage regimen, in which **rifalazil** is administered to a patient in an amount between 0.1 and 10 mg over a period of four to fourteen days, a daily regimen, in which **rifalazil** is administered to a patient in a daily amount of between 0.1 and 5 mg over a period of one. . . includes the step of administering to the patient an average initial daily dose of between 4.5 and 200 mg/day of **rifalazil.** Following the initial daily dose, maintenance doses of **rifalazil** are given to the patient

to sustain a desired tissue concentration of **rifalazil** in the patient. For example, the maintenance doses can themselves be a low-dosage or daily regimen.

DETD [0096] **Rifalazil** formulations and compositions described herein may also include a second therapeutic agent, including for example, another antibiotic, an anesthetic, an. . .

DETD [0097] Antibiotics that can be admixed with the low-dosage **rifalazil** formulation include: aminoglycosides, such as amikacin, apramycin, arbekacin, bambermycins, butirosin, dibekacin, dihydrostreptomycin, fortimicin(s), fradiomycin, gentamicin, ispamicin, kanamycin, micronomicin, neomycin, neomycin. . .

DETD . . . of therapy (treatment or prophylaxis), the anticipated duration, and the severity of the infection or disease for which a low-dosage **rifalazil** formulation is being administered. Additional considerations in dose selection include the type of infection, age of the patient (e.g., pediatric,. . . Determining what concentrations to employ are within the skills of the pharmacist, medicinal chemist, or medical practitioner formulating the low-dosage **rifalazil** in combination with other therapeutic agents.

DETD [0103] The **rifalazil** compositions and therapeutic regimens described herein can be used to treat or prevent bacterial infections as well as diseases associated. . .

DETD [0106] Diseases associated with bacterial infections include, but are not limited to, **atherosclerosis**, multiple sclerosis, rheumatoid arthritis, diabetes, Alzheimer's disease, asthma, cirrhosis of the liver, psoriasis, meningitis, cystic fibrosis, cancer, and osteoporosis.

DETD . . . occur in immuno-compromised individuals by treating the non-multiplying form of the infection in an individual in need thereof, by administering **rifalazil**, or **rifalazil** in conjunction with an antibiotic effective against multiplying bacteria. Progress of the treatment can be evaluated, using the diagnostic tests. . .

DETD . . . bowel disease, ulcerative colitis, and Crohn's disease and vascular inflammatory pathologies, such as, but not limited to, disseminated intravascular coagulation, **atherosclerosis**, and Kawasaki's pathology are also suitable for treatment by methods described herein. The invention can also be used to treat inflammatory diseases such as coronary **artery** disease, hypertension, **stroke**, asthma, chronic hepatitis, multiple sclerosis, peripheral neuropathy, chronic or recurrent sore throat, laryngitis, tracheobronchitis, chronic vascular headaches (including migraines, cluster. . .

DETD . . . subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 5 mg of **rifalazil.**

DETD . . . or may be oily solutions for administration in the form of nasal drops, or as a gel. The concentration of **rifalazil** in the formulation will vary depending upon a number of factors, including the dosage of the drug to be administered,. . .

DETD [0119] **Rifalazil** may optionally be formulated as a pharmaceutically acceptable salt, such as a non-toxic acid addition salts or metal complexes that. . .

DETD [0121] **Rifalazil** may optionally be formulated for controlled release. Many strategies can be pursued to obtain controlled release in which the rate. . .

DETD . . . The methods and compositions of the present invention can be disclosed in the form of instructions for the administration of **rifalazil** in a loading-dose regimen. Typically, the method is disclosed to a patient along with the sale or distribution of **rifalazil.** In some instances, instructions may be included on a

label or on a package insert accompanying a pharmaceutical formulation containing **rifalazil**. The method of the present invention can be incorporated into a prepackaged therapeutic regimen designed to deliver a loading-dose regimen of **rifalazil** to a patient using the prepackaged regimen. For example, **rifalazil** can be packaged in dosage units containing varying quantities of **rifalazil** along with instructions to the patient to administer the larger quantities followed by the smaller quantities over a particular time. . .

DETD **ABI-1648**-006 Clinical Trial

DETD [0125] A clinical trial was conducted to monitor the safety and pharmacokinetics of low doses of **rifalazil** in humans. For these clinical studies, described below, hard gelatin capsules containing microgranulated **rifalazil** (as described in U.S. Pat. No. 5,547,683) were prepared at several different strengths: 2.5 mg, 5 mg, 12.5 mg, and. . .

DETD [0126] **Rifalazil** was administered to 80 patients in a randomized trial at single doses of 2.5 mg (see FIGS. 1A and 1B),. . .

DETD . . . various dosing regimens based upon the experimentally derived pharmacokinetic parameters. Equation 5 is then used to calculate the amount of **rifalazil** in the plasma compartment. Low-dosage regimens are simulated using constants derived from PK parameters for 2.5 mg oral dose in. . .

DETD . . . Vdβ is the volume of distribution; F is the fraction of administered dose absorbed; and A.sub.T is the amount of **rifalazil** in the tissue compartment.

TABLE 1

Dose-normalized pharmacokinetic parameters for males following oral administration of single 2.5 mg and 50 mg doses of **rifalazil**.

Parameters	Dosing Level 2.5 mg	50 mg
C.sub.max (ng/mL)	7.9	57.3
AUC (ng/mL + hr)	185.2	1347
Absorption t1/2. . .		

DETD . . . (PK) parameters derived for 2.5 mg oral dosing in male subjects and equations 1-12 above, the simulated plasma and tissue **rifalazil** concentrations were calculated for a single 2.5 mg oral; a single 1.0 mg oral; a single 0.25 mg oral; five daily 1.0 mg oral; and five daily 0.25 mg oral **rifalazil** administrations (Table 1). The simulations are based on the pharmacokinetic parameters derived from the plasma concentration data following administration of a single 2.5 mg dose of **rifalazil** and is based on an assumed bioavailability of 25% (the actual bioavailability in man is currently unknown but this value. . .

DETD [0133] At 2.5 mg single dose, the simulated PK curve shows that the tissue concentration of **rifalazil** remains above the MIC for C. trachomatis for greater than 500 hours (FIG. 3).

DETD [0134] At 1.0 mg single dose, the simulated PK curve shows that the plasma and tissue concentrations of **rifalazil** remains above the MIC for C. trachomatis for greater than 48 and 350 hours, respectively (FIG. 4).

DETD [0135] At 0.25 mg single dose, the simulated PK curve shows that the plasma and tissue concentrations of **rifalazil** remains above the MIC for C. trachomatis for greater than 24 and 96 hours, respectively (FIG. 5).

DETD . . . dose regimen of 1.0 mg daily for 5 days, the simulated PK curve

shows that plasma and tissue concentrations of **rifalazil** remain above the MIC for C. trachomatis for greater than 336 hours and 3 weeks, respectively (FIG. 6).

DETD . . . dose regimen of 0.25 mg daily for 5 days, the simulated PK curve shows that plasma and tissue concentrations of **rifalazil** remain above the MIC for C. trachomatis for 24 hours and 480 hours, respectively (FIG. 7).

CLM What is claimed is:

1. A pharmaceutical composition comprising a unit dosage form of **rifalazil** in an amount between 0.1 and 5 mg.

2. The pharmaceutical composition of claim 1, wherein said unit dosage comprises **rifalazil** in an amount between 0.1 and 3 mg.

3. The pharmaceutical composition of claim 2, wherein said unit dosage comprises **rifalazil** in an amount between 0.1 and 1 mg.

4. The pharmaceutical composition of claim 3, wherein said unit dosage comprises **rifalazil** in an amount between 0.2 and 0.8 mg.

6. A method of treating a bacterial infection in a patient, said method comprising administering **rifalazil** to said patient in an amount effective to treat said infection, wherein said **rifalazil** is formulated in unit dosages comprising between 0.1 and 5 mg of **rifalazil.**

8. The method of claim 6, wherein **rifalazil** is administered for prophylaxis against an infection resulting from a surgical procedure or implantation of a prosthetic device.

16. The method of claim 6, wherein said **rifalazil** is formulated in unit dosages comprising between 0.1 and 3 mg of **rifalazil.**

17. The method of claim 16, wherein said **rifalazil** is formulated in unit dosages comprising between 0.1 and 2 mg of **rifalazil.**

18. The method of claim 17, wherein said **rifalazil** is formulated in unit dosages comprising between 0.2 and 0.8 mg of **rifalazil.**

19. The method of claim 6, wherein said **rifalazil** is formulated as a tablet, pill, capsule, or caplet.

. . . treating a bacterial infection in a patient, said method comprising administering to said patient between 0.1 and 10 mg of **rifalazil** over a period of four to fourteen days.

21. The method of claim 20, wherein between 0.1 and 5 mg of **rifalazil** is administered over a period of four to ten days.

. . . treating a bacterial infection in a patient, said method comprising administering to said patient between 0.1 and 5 mg of **rifalazil** daily for at least a period of two days.

23. The method of claim 22, wherein between 0.1 and 3 mg of **rifalazil** is administered daily for at least a period of five days.

24. The method of claim 23, wherein between 0.1 and 2.6 mg of **rifalazil** is administered daily for at least a period of ten days.

25. The method of claim 24, wherein between 0.1 and 1.6 mg of **rifalazil** is administered daily for at least a period of thirty days.

26. A method of treating a bacterial infection in a patient, said method comprising administering a loading-dose regimen of **rifalazil** to said patient.

30. A method for treating or preventing the development of an **atherosclerosis**-associated disease in a patient in need thereof, said method comprising administering **rifalazil** to said patient in an amount effective to treat or prevent the development of said **atherosclerosis**-associated disease in said patient, wherein said **rifalazil** is formulated in unit dosages comprising between 0.1 and 5 mg of **rifalazil.**

38. The method of claim 30, wherein said **atherosclerosis** -associated disease is coronary **artery** disease, **myocardial** infarction, **angina** pectoris, **stroke** , **cerebral ischemia**, intermittent **claudication**, **gangrene**, mesenteric **ischemia**, temporal **arteritis**, or renal **artery** stenosis.

. . . 39. The method of claim 30, wherein, prior to administration of said compound, said patient is diagnosed as having said **atherosclerosis**-associated disease.

. . . the level of C-reactive protein in a patient identified as having increased levels of C-reactive protein, said method comprising administering **rifalazil** to said patient in an amount sufficient to reduce the level of C-reactive protein, wherein said **rifalazil** is formulated in unit dosages comprising between 0.1 and 5 mg of **rifalazil.**

. . . for reducing Chlamydia pneumoniae replication in macrophages or foam cells in a patient in need thereof, said method comprising administering **rifalazil** to said patient in an amount effective to reduce Chlamydia pneumoniae replication in macrophages or foam cells in said patient, wherein said **rifalazil** is formulated in unit dosages comprising between 0.1 and 5 mg of **rifalazil.**

. . . method for treating a persistent Chlamydia pneumoniae infection in macrophages or foam cells in a patient, said method comprising administering **rifalazil** to said patient in an amount effective to treat said Chlamydia pneumoniae infection in macrophages or foam cells in said patient, wherein said **rifalazil** is formulated in unit dosages comprising between 0.1 and 5 mg of **rifalazil.**,

. . . infection of a bacterium having a multiplying form and a non-multiplying form, said method comprising administering to a patient (i) **rifalazil**; and (ii) a second antibiotic effective against the multiplying form of said bacterium, wherein said **rifalazil** is administered in an amount and for a duration effective to treat the non-multiplying form of said bacterium and the. . . . administered in an amount and for a duration effective to treat said multiplying form of said bacterium and wherein said **rifalazil** is formulated in unit dosages comprising between 0.1 and 5 mg of **rifalazil.**

. . . for a duration to reduce the presence of said bacterium in said patient to less than about 10.sup.6 organisms/mL; and **rifalazil** is then administered to said patient in an amount and for a duration effective to reduce the presence of said. . .

. . . method of eradicating non-multiplying bacteria not eradicated in a patient following treatment with a first antibiotic, said method comprising administering **rifalazil** to said patient in an amount and for a duration effective to eradicate said non-multiplying bacteria in said patient, wherein said **rifalazil** is formulated in unit dosages comprising between 0.1 and 5 mg of **rifalazil.**

. . . disease associated with a bacterial infection caused by bacteria capable of establishing a non-multiplying form phase, said method comprising administering **rifalazil** to said patient in an amount and for a duration effective to treat said patient, wherein said **rifalazil** is formulated in unit dosages comprising between 0.1 and 5 mg of **rifalazil.**

48. A method of treating the cryptic phase of a bacterial infection, said method comprising administering **rifalazil** to said patient in an amount and for a duration effective to treat said cryptic phase of said bacterial infection, wherein said **rifalazil** is formulated in unit dosages comprising between 0.1 and 5 mg of **rifalazil.**

49. A pharmaceutical formulation comprising **rifalazil**, wherein said formulation is packaged with a label or package insert providing instructions for the use of said formulation, said instructions describing administration of said **rifalazil** using a loading-dose regimen.

. . . of claim 49, wherein said formulation is provided in a prepackaged therapeutic regimen comprising: a) a first dosage unit comprising **rifalazil**; b) a second dosage unit comprising a smaller dose of **rifalazil** than said first dosage unit; c) instructions for the administration of said first dosage unit prior to said second dosage. .

51. The prepackaged regimen of claim 50, wherein said second dosage unit comprises between 0.1 and 5.0 mg of **rifalazil.**

L160 ANSWER 16 OF 21 USPATFULL on STN
ACCESSION NUMBER: 2004:83262 USPATFULL
TITLE: Targeted therapeutics and uses thereof
INVENTOR(S): **Michaelis, Arthur F.**, Devon, PA, UNITED STATES
Maulding, Hawkins V., Mendham, NJ, UNITED STATES
Sayada, Chalom, Luxembourg City, LUXEMBOURG
Zha, Congxiang, Schenectady, NY, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004063718	A1	20040401	
APPLICATION INFO.:	US 2002-302409	A1	20021121	(10)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2002-358881P	20020222	(60)
	US 2001-332264P	20011121	(60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: CLARK & ELBING LLP, 101 FEDERAL STREET, BOSTON, MA, 02110
NUMBER OF CLAIMS: 35
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Page(s)
LINE COUNT: 1997
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention features a method of delivering a drug to a diseased cell by linking the drug to a rifamycin derivative, compositions that include drug-rifamycin conjugates of the invention, and methods for treating disease using those compositions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IN **Michaelis, Arthur F.**, Devon, PA, UNITED STATES
IN **Sayada, Chalom**, Luxembourg City, LUXEMBOURG

SUMM [0040] The invention further features a method for treating or preventing the development of an **atherosclerosis**-associated disease in a patient by administering to the patient a compound of the invention, wherein therapeutic drug (B) is an. . . blood thinning agent, or a lipid lower agent, in an amount effective to treat or prevent the development of the **atherosclerosis**-associated disease in the patient.

SUMM [0073] By "**atherosclerosis**" is meant the progressive accumulation of smooth muscle cells, inflammatory cells, lipid products (e.g., lipoproteins, or cholesterol), cellular waste products, calcium, or other substances within the inner lining of an **artery**, resulting in the narrowing or obstruction of the blood vessel and the development of **atherosclerosis**-associated diseases. **Atherosclerosis** is typically manifested within large and medium-sized **arteries**, and is often characterized by a state of chronic inflammation within the **arteries.**

SUMM [0074] By "**atherosclerosis**-associated disease" is meant any disorder that is caused by or is associated with **atherosclerosis** . Typically, **atherosclerosis** of the coronary **arteries** commonly causes coronary **artery** disease, **myocardial** infarction, coronary thrombosis, and **angina** pectoris. **Atherosclerosis** of the **arteries** supplying the central nervous system frequently provokes **strokes** and transient **cerebral ischemia.** In the peripheral circulation, **atherosclerosis** causes intermittent **claudication** and **gangrene** and can jeopardize limb viability. **Atherosclerosis** of an **artery** of the splanchnic circulation can cause mesenteric **ischemia.** **Atherosclerosis** can also affect the kidneys directly (e.g., renal **artery** stenosis).

SUMM [0075] A patient who is being treated for an **atherosclerosis** -associated disease is one who a medical practitioner has diagnosed as having such a disease. Diagnosis may be by any suitable means. Methods for diagnosing **atherosclerosis** by measuring systemic inflammatory markers are described, for example, in U.S. Pat. No. 6,040,147, hereby incorporated by reference. Diagnosis may employ an **electrocardiogram**, chest X-ray, **echocardiogram**, **cardiac** catheterization, or measurement of blood levels of CPK, CPK-MB, myoglobin, troponin, homocysteine, or C-reactive protein. A patient in whom the development of an **atherosclerosis** -associated disease is being prevented is one who has not received such a diagnosis. One in the art will understand that these patients may have been subjected to the same tests (**electrocardiogram**, chest X-ray, etc.) or may have been identified, without examination, as one at

high risk due to the presence of. . . cholesterol levels). Thus, prophylactic administration of a compound of the invention is considered to be preventing the development of an **atherosclerosis**-associated disease.

SUMM [0076] An **atherosclerosis**-associated disease has been treated or prevented when one or more tests of the disease (e.g., any of the those described. . . or the patient's risk is reduced. In one example, a reduction in C-reactive protein to normal levels indicates that an **atherosclerosis**-associated disease has been treated or prevented.

DETD . . . agent, or a lipid lower agent, the resulting (A)-(L)-(B) conjugate is useful for treating or preventing the development of an **atherosclerosis**-associated disease. The conjugate, when administered to a patient suffering from **atherosclerosis**-associated disease, lowers the level of C-reactive protein in the patient.

DETD . . . in the art. These include but are not limited to assays for monitoring inflammation, microbial infection, and autoimmune diseases (e.g., **atherosclerosis**, MS, rheumatoid arthritis).

DETD [0151] In addition, compounds can be evaluated using standard in vivo animal models of infection and autoimmune disease (e.g., **atherosclerosis**, MS, rheumatoid arthritis).

DETD . . . other animals with a pharmaceutically acceptable diluent, carrier, or excipient, in unit dosage form. Administration may be topical, parenteral, intravenous, intra-**arterial**, subcutaneous, intramuscular, intracranial, intraorbital, ophthalmic, intraventricular, intracapsular, intraspinal, intracisternal, intraperitoneal, intranasal, aerosol, by suppositories, or oral administration.

DETD [0168] The selective oxidation of the 30 and 32 positions of **Rifalazil** from H to OH is shown in reaction scheme 1. This transformation can be achieved by enzymatic oxidation using the. . . diisopropylfluorophosphate, diethyl p-nitrophenylphosphate, or eserine, can be added to prevent enzymatic deacetylation of the rifamycin derivative. 30-Hydroxy Rifalizil and 32-hydroxy **Rifalazil** can be separated using the hplc techniques described in Mae et al., Xenobiotica, 30(6):565, 2000.

DETD . . . U.S. Pat. No. 4,585,589, hereby incorporated by reference. For example, the acid halide of pyrazinoic acid can be reacted with **Rifalazil.** Using the conditions described in U.S. Pat. No.4,585,589, the phenolic hydroxyl group can be selectively acylated, as shown in reaction. . .

DETD [0227] ABI 0027 is a zero-length linker conjugate of **rifalazil** and isonicotinic acid. Conjugation to **rifalazil** modifies the biodistribution of isonicotinic acid in a manner that can enhance its antimicrobial activity.

DETD [0229] To a solution of **Rifalazil** (9.5 g, 10 mmol) in DMF (100 mL) was added 2,2-dimethoxypropane (60 mL, 484 mmol) and camphorsulfonic acid (CSA, 0.20. . .

DETD [0234] ABI 0029 is is a zero-length linker conjugate of **rifalazil** and isonicotinic acid. Conjugation to **rifalazil** modifies the biodistribution of isonicotinic acid in a manner that can enhance its antimicrobial activity. ##STR73##

DETD [0236] Potassium methoxide (447 mg, 6.39 mmol) was added to a solution of **Rifalazil** (2.0 g, 2.1 mmol) in methanol (20 mL) at room temperature and then stirred overnight. The reaction was then diluted. . .

CLM What is claimed is:

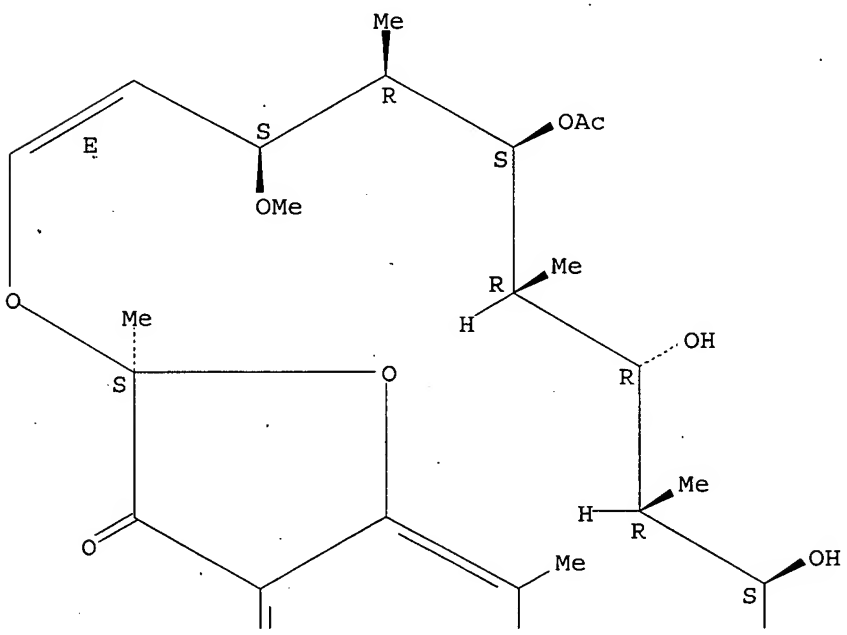
30. A method for treating or preventing the development of an **atherosclerosis**-associated disease in a patient in need thereof,

said method comprising administering a compound of claims 1, 4, or 11 to said patient a composition in an amount effective to treat or prevent the development of said **atherosclerosis**-associated disease in said patient.

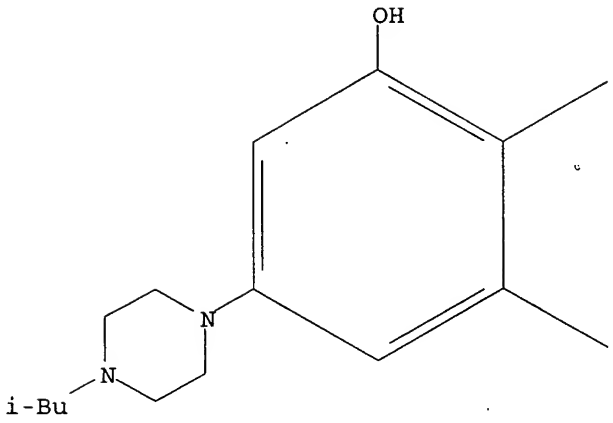
IT 77-76-9, 2,2-Dimethoxypropane 14254-57-0, Isonicotinoyl chloride 39178-35-3, Isonicotinoyl chloride hydrochloride **129791-92-0**, Rifalazil
(preparation of drug conjugate with rifamycin derivative as targeting moiety)
IT **129791-92-0**, Rifalazil
(preparation of drug conjugate with rifamycin derivative as targeting moiety)
RN 129791-92-0 USPATFULL
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

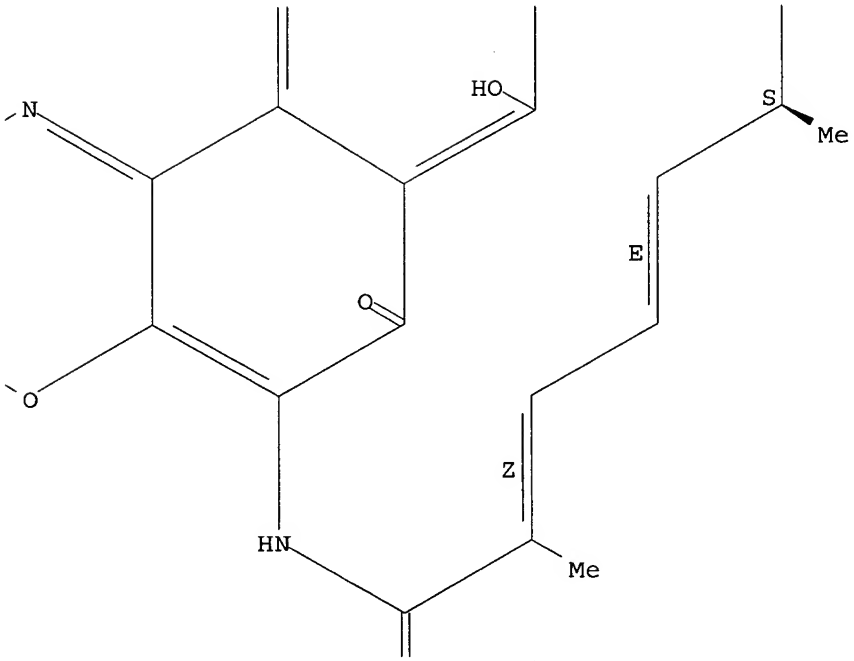
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

O

L160 ANSWER 17 OF 21 USPATFULL on STN
ACCESSION NUMBER: 2004:45028 USPATFULL
TITLE: Intravenous **rifalazil** formulation and methods of use thereof

INVENTOR(S): **Michaelis, Arthur F.**, Devon, PA, UNITED STATES
Sayada, Chalom, Luxembourg City, LUXEMBOURG
Cabana, Bernard E., Montgomery Village, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004034021	A1	20040219
APPLICATION INFO.:	US 2003-453155	A1	20030603 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-385532P	20020603 (60)
	US 2002-406873P	20020829 (60)
	US 2002-412958P	20020923 (60)
	US 2003-444570P	20030203 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: CLARK & ELBING LLP, 101 FEDERAL STREET, BOSTON, MA, 02110
NUMBER OF CLAIMS: 62
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Page(s)
LINE COUNT: 1942
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention features intravenous dosage formulations of **rifalazil** and methods of treating disease by intravenous administration of **rifalazil.**

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Intravenous **rifalazil** formulation and methods of use thereof
IN **Michaelis, Arthur F.**, Devon, PA, UNITED STATES
IN **Sayada, Chalom**, Luxembourg City, LUXEMBOURG
IN **Cabana, Bernard E.**, Montgomery Village, MD, UNITED STATES
AB The invention features intravenous dosage formulations of **rifalazil** and methods of treating disease by intravenous administration of **rifalazil.**
SUMM [0004] One agent capable of treating a wide variety of infections is **rifalazil. Rifalazil** is described in the U.S. Pat. No. 4,983,602, where its antibacterial activity is disclosed.
SUMM [0005] We have discovered methods of formulating **rifalazil** for intravenous administration, as well as developing compositions thereof, and methods of treating disease by administering **rifalazil** intravenously.
SUMM [0006] In one aspect, the invention features an aqueous solution of **rifalazil** suitable for intravenous administration to a human, wherein the solution has a **rifalazil** concentration of between 10 and 10,000 μg/mL. Desirably, the solution has a **rifalazil** concentration of between 10 and 5,000, 10 and 3,000, 50 and 10,000, 50 and 2,000, 100 and 10,000, 100 and. . .
SUMM [0007] The aqueous solution of **rifalazil** may contain one or more excipients. Particular excipients that may be used in the preparation of **rifalazil** solutions include polyethoxylated fatty acids, PEG-fatty acid diesters, PEG-fatty acid mono-ester and di-ester mixtures, polyethylene glycol glycerol fatty acid esters,. . . esters, lower alcohol fatty acid esters, and ionic surfactants. Any excipient described herein can be used in the formulation of **rifalazil.** Desirably, the aqueous solutions of **rifalazil** include one or more excipients selected from sodium lauryl sulfate,

polyoxyl-40 stearate, PEG-3 castor oil, PEG-5 castor oil, PEG-9 castor. . .

SUMM [0008] The invention also features an aqueous composition for inhibiting the hydrolytic degradation of **rifalazil** dissolved therein. The composition includes **rifalazil**, water, and a micelle-forming excipient.

SUMM . . . features a method of treating disease in a human. This method includes the intravenous administration of an aqueous solution of **rifalazil** to a human in an amount effective to treat the disease. The aqueous solution of **rifalazil** is formulated as described herein and is suitable for administration to a human.

SUMM [0010] The methods of the invention can be used to treat any disease or infection for which **rifalazil** is effective including, for example, community-acquired pneumonia, upper and lower respiratory tract infection, skin and soft tissue infection, bone and. . .

SUMM . . . used to treat diseases associated with bacterial infection. For example, bacterial infections can produce inflammation resulting in the pathogenesis of **atherosclerosis**, multiple sclerosis, rheumatoid arthritis, diabetes, Alzheimer's disease, asthma, cirrhosis of the liver, psoriasis, meningitis, cystic fibrosis, cancer, and osteoporosis. Accordingly, the invention features a method of treating such diseases, among others, by administering **rifalazil** intravenously.

SUMM [0012] The invention also includes the preoperative intravenous administration of **rifalazil** to reduce or eliminate the incidence of postoperative infections in patients undergoing surgical procedures or implantation of prosthetic devices.

SUMM . . . aspect, the invention features a method of treating a non-mycobacterial infection by Gram-positive bacteria in a human patient by administering **rifalazil** to the patient in an amount effective to treat the infection. The Gram-positive bacterial infections to be treated include, without. . .

SUMM . . . the invention features a method of treating an infection by multi-drug resistant bacteria in a human by intravenous administration of **rifalazil** to the human in an amount effective to treat the infection. Resistant strains of bacteria include penicillin-resistant, methicillin-resistant, quinolone-resistant, macrolide-resistant,. . .

SUMM . . . spp., Rickettsia spp., Spirochaeta spp., Legionella spp., Mycobacteria spp., Ureaplasma spp., Streptomyces spp., and Trichomoras spp. In this method, intravenous **rifalazil** is administered to the patient in an amount effective to treat or ameliorate the bacterial infection, or is administered prophylactically. . .

SUMM . . . method of treating an intracellular infection by a facultative or obligate intracellular microbe. The method includes the intravenous administration of **rifalazil** in an amount effective to treat the intracellular infection. The microbe can be a bacterium, fungus, protozoan, or virus. Infections. . .

SUMM . . . as being infected with a bacterium having a multiplying form and a non-multiplying form by administering to the patient (i) **rifalazil** intravenously, and (ii) a second antibiotic that is effective against the multiplying form of the bacterium, wherein the two antibiotics. . .

SUMM . . . 3 days, but may take as long as a week. After this has been achieved, the patient is then administered **rifalazil** intravenously in an amount and for a duration effective to complete the treatment of the patient. Antibiotics that are effective. . .

SUMM . . . with a bacterial infection caused by bacteria capable of establishing a cryptic phase. The method includes the step of administering **rifalazil** intravenously to the patient.

SUMM . . . features a method of treating the cryptic phase of a bacterial

infection. This method includes the step of administering intravenous **rifalazil** to a patient. The administering is for a time and in an amount effective to treat the cryptic phase of. . .

SUMM . . . and an amount effective to treat the multiplying form, and (b) treating the non-multiplying form of the bacteria by administering **rifalazil** intravenously to the patient, wherein the administering is for a time and in an amount effective to treat the non-multiplying. . .

SUMM [0024] The invention also features a method for treating or preventing the development of an **atherosclerosis**-associated disease in a human patient. The method includes the intravenous administration of **rifalazil** in an amount effective to treat or prevent the development of the **atherosclerosis**-associated disease in the patient. The patient is typically diagnosed as having the **atherosclerosis**-associated disease (or being at increased risk of developing the disease) or as having macrophages or foam cells infected with C. pneumoniae prior to the intravenous administration of **rifalazil.**

SUMM . . . reducing the level of C-reactive protein in a human patient in need thereof. This method includes the intravenous administration of **rifalazil** in an amount effective to reduce the level of C-reactive protein in the patient. In one embodiment, the patient has. . .

SUMM . . . replication in macrophages or foam cells in a human patient in need thereof. This method includes the intravenous administration of **rifalazil** in an amount effective to reduce C. pneumoniae replication in macrophages or foam cells in the patient.

SUMM . . . persistent C. pneumoniae infection in macrophages or foam cells in a human patient. The method includes the intravenous administration of **rifalazil** in an amount effective to treat the C. pneumoniae infection in macrophages or foam cells in the patient.

SUMM . . . a method for treating a chronic disease associated with an infection of C. pneumoniae. This method includes intravenous administration of **rifalazil** in an amount effective to treat the infection.

SUMM . . . infection of C. difficile, or preventing the disease or infection in the patient. The method includes the intravenous administration of **rifalazil** to the patient in an amount effective to treat the infection. The method may be employed as an initial treatment. . .

SUMM [0030] In any of the above treatment or prevention methods, **rifalazil** is administered intravenously. The intravenously administered **rifalazil** is formulated as an aqueous that includes **rifalazil** at a concentration of between 10 and 10,000 μg/mL, water, and one or more solubility enhancing pharmaceutically acceptable excipients.

SUMM [0031] If desired, **rifalazil** may be administered in conjunction with one or more additional agents such as anti-inflammatory agents (e.g., non-steroidal anti-inflammatory drugs (NSAIDs;. . . may be administered within 14 days, 7 days, 1 day, 12 hours, or 1 hour of the intravenous administration of **rifalazil**, or simultaneously therewith. The additional therapeutic agents may be present in the same or different pharmaceutical compositions as the intravenous formulation of **rifalazil.** When present in different pharmaceutical compositions, different routes of administration may be used. For example, a second agent may be administered orally or by intramuscular or subcutaneous injection. Agents that can be administered in conjunction with **rifalazil** include any of the agents described herein.

SUMM [0032] For any of the methods described herein, **rifalazil** can

be administered by intravenous infusion, wherein between 1 and 48 mg of **rifalazil** is administered over a period of 4 to 24 hours. Desirably, between 1 and 40 mg, 1 and 30 mg, 2 and 30 mg, 3 and 30 mg, or 4 and 25 mg of **rifalazil** is administered over a period of 4 to 24 hours, 8 to 24 hours, or 15 to 24 hours. Up. . . 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, or 50 mg of **rifalazil** is administered by intravenous infusion over a 2, 4, 5, 6, 7, 8, 9, 10, 12, 14, 20, 24, 48,. . .

SUMM [0033] For any of the methods described herein, **rifalazil** can be administered by intravenous bolus of between 2 and 25 mg of **rifalazil** over a 10 to 60 minute period followed by a slow infusion of 0.1 to 2 mg, 0.5 to 2. . .

SUMM [0034] The intravenous administration of **rifalazil** may be repeated as needed. For example, the administration may be repeated daily, or every other day, for a period. . .

SUMM . . . another aspect, the invention features a method of treating disease in a human. The method includes the intravenous administration of **rifalazil** at a rate that maintains a plasma concentration of **rifalazil** of between 2 and 100, 2 and 80, 2 and 60, 2 and 30, 6 and 50, or 10 and. . .

SUMM [0036] Desirably, **rifalazil** is administered in a dosing regimen that maintains a plasma concentration of **rifalazil** of between 2 and 100, 2 and 60, or 2 and 40 ng/mL for a period greater than 24 hours.

SUMM [0037] The invention also features a pharmaceutical formulation for intravenous administration including **rifalazil.** The formulation includes an aqueous solution of **rifalazil** and is packaged with a label or package insert providing instructions for the use of the formulation wherein the instructions. . .

SUMM [0038] The compositions can also be packaged as a concentrate including **rifalazil** and micelle-forming excipient. The concentrate optionally includes some water. For example, the concentrate can be less than 40%, 20%, 10%,. . . water by volume. The concentrate contains greater than 100 μg/mL, 1 mg/mL, 5 mg/mL, 10 mg/mL, or 20 mg/mL of **rifalazil.**

SUMM [0041] By "effective" amount is meant the amount of **rifalazil** required to treat or prevent an infection or a disease associated with an infection. The effective amount of **rifalazil** used to practice the invention for therapeutic or prophylactic treatment of conditions caused by or contributed to by a microbial. . .

SUMM . . . greater than 40% water by volume and without undissolved solids above 0.5 microns in size. Desirably, the aqueous solutions of **rifalazil** include greater than 60%, 70%, 80%, 90%, 95%, 97%, or even 98% water (w/w) and the **rifalazil** is completely dissolved. **Rifalazil** can be dissolved in either an aqueous phase or a micellar phase of the aqueous solution.

SUMM [0045] By "an aqueous composition for inhibiting the hydrolytic decomposition of **rifalazil**" is meant an aqueous solution in which less than ten percent of the **rifalazil** is degraded to des-acetyl **rifalazil** at 25° C. over a one year period.

SUMM [0046] As used herein, "suitable for intravenous administration to a human" refers to an aqueous solution including **rifalazil** and one or more pharmaceutically acceptable excipients. Solutions that are suitable for intravenous administration to a human do not include. . . of aqueous solutions of insoluble compounds. However, these organic solvents are poisons in the amounts required for the formulation of **rifalazil** and, therefore, could not be administered intravenously to a patient without compromising the health of the patient. Furthermore, solutions that. . .

SUMM [0047] By "bolus" injection or administration is meant intravenous

administration of **rifalazil** wherein a dose of greater than 2 mg of **rifalazil** is administered over a period of less than one hour.

SUMM [0048] By "infusion" is meant a continuous intravenous administration of **rifalazil** over a period of greater than one hour wherein **rifalazil** is administered at a constant rate of less than or equal to 2 mg of **rifalazil** per hour.

SUMM [0049] By "**atherosclerosis**" is meant the progressive accumulation of smooth muscle cells, immune cells (e.g., lymphocytes, macrophages, or monocytes), lipid products (e.g., lipoproteins, or cholesterol), cellular waste products, calcium, or other substances within the inner lining of an **artery**, resulting in the narrowing or obstruction of the blood vessel and the development of **atherosclerosis**-associated diseases. **Atherosclerosis** is typically manifested within large and medium-sized **arteries**, and is often characterized by a state of chronic inflammation within the **arteries.**

SUMM [0050] By "**atherosclerosis**-associated disease" is meant any disorder that is caused by or is associated with **atherosclerosis**. Typically, **atherosclerosis** of the coronary **arteries** commonly causes coronary **artery** disease, **myocardial** infarction, coronary thrombosis, and **angina** pectoris. **Atherosclerosis** of the **arteries** supplying the central nervous system frequently provokes **strokes** and transient **cerebral ischemia.** In the peripheral circulation, **atherosclerosis** causes intermittent **claudication** and **gangrene** and can jeopardize limb viability. **Atherosclerosis** of an **artery** of the splanchnic circulation can cause mesenteric **ischemia.** **Atherosclerosis** can also affect the kidneys directly (e.g., renal **artery** stenosis).

SUMM [0051] A human patient who is being treated for an **atherosclerosis**-associated disease is one who a medical practitioner has diagnosed as having such a disease. Diagnosis may be by any suitable means. Methods for diagnosing **atherosclerosis** by measuring systemic inflammatory markers are described, for example, in U.S. Pat. No. 6,040,147, hereby incorporated by reference. Diagnosis and monitoring may employ an **electrocardiogram**, chest X-ray, **echocardiogram**, **cardiac** catheterization, ultrasound (for the measurement of vessel wall thickness), or measurement of blood levels of CPK, CPK-MB, myoglobin, troponin, homocysteine, or C-reactive protein. A patient in whom the development of an **atherosclerosis**-associated disease is being prevented is one who has not received such a diagnosis. One in the art will understand that these patients may have been subjected to the same tests (**electrocardiogram**, chest X-ray, etc.) or may have been identified, without examination, as one at high risk due to the presence of one or more risk factors (e.g., family history, hypertension, diabetes mellitus, high cholesterol levels). Thus, prophylactic intravenous administration of **rifalazil** is considered to be preventing the development of an **atherosclerosis**-associated disease.

SUMM [0052] An **atherosclerosis**-associated disease has been treated or prevented when one or more tests of the disease (e.g., any of the those described. . . . improved or the patient's risk reduced. In one example, a reduction in C-reactive protein to normal levels indicates that an **atherosclerosis**-associated disease has been treated or prevented.

SUMM . . . of C. pneumoniae. Any suitable method may be employed (e.g., determination of C. pneumoniae in blood monocytes or in the **atheroma** itself (e.g., in macrophages or foam cells present in

the fatty streak), or detection of C. pneumoniae DNA, RNA, or. . .

SUMM . . . These organisms cause diarrhea. Antibiotic-associated bacterial diarrhea includes such conditions as C. difficile associated diarrhea (CDAD) and pseudomembranous colitis. When **rifalazil** is administered intravenously for the treatment of a C. difficile infection, an effective amount of **rifalazil** is the amount required to eradicate C. difficile from the patient, or the amount which prevents an infection of C.. . .

SUMM . . . mononuclear cells (e.g., macrophages, lymphocytes, and plasma cells), tissue destruction, and fibrosis. Non-limiting examples of inflammatory disease include asthma, coronary **artery** disease, arthritis, conjunctivitis, lymphogranuloma venerum, and salpingitis.

DRWD [0074] FIG. 1 is a graph of the solubility of **rifalazil** in water as a function of pH.

DRWD [0075] FIG. 2 is a graph depicting the solubility of **rifalazil** in solvent-water mixtures.

DRWD [0076] FIG. 3 is a graph depicting the influence of solubilizing agents on the solubility of **rifalazil** in water.

DRWD [0077] FIG. 4 is a graph depicting the solubility of **rifalazil** in aqueous solutions containing lipophilic salts. DTAB=dodecyltrimethylammonium bromide; Cheno=sodium chenodeoxycholate; Octyl=sodium octylsulfate; Deoxy=sodium deoxycholate; Cholate=sodium cholate; SDS=sodium dodecylsulfate.

DRWD [0078] FIG. 5 is a graph depicting the solubility of **rifalazil** in aqueous solutions containing varying amounts of sodium dodecylsulfate at pH 5.4 and 7.4.

DRWD [0079] FIG. 6 is a graph depicting the solubility of **rifalazil** in aqueous solutions containing varying amounts of PEG-35 castor oil.

DRWD [0080] FIG. 7 is a graph depicting the hydrolytic degradation of **rifalazil** in the presence of the micelle-forming excipient PEG-35 castor oil as a function of time.

DRWD [0081] FIG. 8 is a graph depicting the hydrolytic degradation of **rifalazil** in the absence of a micelle-forming excipient as a function of time.

DETD [0082] In general, the invention provides aqueous solutions of **rifalazil** that are suitable for intravenous administration to a human. The aqueous solutions include one or more excipients that enhance the solubility and inhibit the hydrolytic degradation of **rifalazil.**

DETD [0083] For the treatment of many nosocomial and serious community acquired infections, it is often desirable to administer **rifalazil** parenterally, because of the lack of predictability in the bioavailability of orally administered **rifalazil** to diseased individuals. Intravenous administration is preferred for the treatment of life-threatening infections, for patients with severe illness, for persistent. . .

DETD [0085] **Rifalazil** is virtually insoluble in water at physiological pH. A typical low dosage concentration of **rifalazil** for intravenous administration is 100 μg/mL, which is 5,000 times greater than the solubility of the drug in water at pH 7 (see FIG. 1). In order to provide a reasonable safety margin for an intravenous dosage form of **rifalazil**, the target solubility at room temperature, allowing for solubility changes due to extremes of temperature, is set at a value. . .

DETD [0086] Another challenge to the use of aqueous formulations of **rifalazil** is the hydrolytic degradation of **rifalazil**, which occurs readily in aqueous environments under ambient conditions (see FIG. 8 and Example 3). To be commercially useful, any. . . a stable and predictable form prior to administration to a human. The formulations described herein overcome the hydrolytic degradation of

rifalazil by the addition of a micelle-forming excipient, which inhibits the degradation of **rifalazil** (see FIG. 7 and Example 3) in comparison to aqueous solutions in the absence of a micelle-forming excipient.

DETD [0087] Solubilizing excipients can be used for the preparation of an intravenous dosage formulation of **rifalazil.** The excipients used are restricted to those that have a high degree of safety in humans.

DETD [0088] As used herein, "solubilization" describes the improvement in the solubility of **rifalazil** resulting from the addition of surface-active compounds to the aqueous solution. The solubilizates formed contain **rifalazil** present in dissolved form in the molecular associations, micelles, of the surface-active compounds, which form in aqueous solution (see FIGS.. . .

DETD [0089] A variety of solubilizers may be used for the formulation of **rifalazil** including those solubilizers disclosed in U.S. Pat. No. 6,365,637, herein incorporated by reference, proteins which readily bind lipophilic compounds such. . .

DETD [0090] Polyethoxylated fatty acids may be used as excipients for the formulation of **rifalazil.** Examples of commercially available polyethoxylated fatty acid monoester surfactants include: PEG 4-100 monolaurate (Crodet L series, Croda), PEG 4-100 monooleate. . . oleate (Albunol 200 MO, Taiwan Surf.), PEG-400 oleate (LACTOMUL, Henkel), and PEG-600 oleate (Albunol 600 MO, Taiwan Surf.). Formulations of **rifalazil** according to the invention may include one or more of the polyethoxylated fatty acids above.

DETD [0091] Polyethylene glycol fatty acid diesters may also be used as excipients for the formulation of **rifalazil.** Examples of commercially available polyethylene glycol fatty acid diesters include: PEG-4 dilaurate (Mapeg® 200 DL, PPG), PEG-4 dioleate (Mapeg® 200. . . (Kessco® PEG 1540 DS, Stepan), PEG-400 dioleate (Cithrol 4DO series, Croda), and PEG-400 distearate Cithrol 4DS series, Croda). Formulations of **rifalazil** according to the invention may include one or more of the polyethylene glycol fatty acid diesters above.

DETD [0092] PEG-fatty acid mono- and di-ester mixtures may be used as excipients for the formulation of **rifalazil.** Examples of commercially available PEG-fatty acid mono- and di-ester mixtures include: PEG 4-150 mono, dilaurate (Kessco® PEG 200-6000 mono, Dilaurate,. . . mono, dioleate (Kessco® PEG 200-6000 mono, Dioleate, Stepan), and PEG 4-150 mono, distearate (Kessco® 200-6000 mono, Distearate, Stepan). Formulations of **rifalazil** according to the invention may include one or more of the PEG-fatty acid mono- and di-ester mixtures above.

DETD [0093] In addition, polyethylene glycol glycerol fatty acid esters may be used as excipients for the formulation of **rifalazil.** Examples of commercially available polyethylene glycol glycerol fatty acid esters include: PEG-20 glyceryl laurate (Tagat® L, Goldschmidt), PEG-30 glyceryl laurate. . . and Aldo® MS-20 KFG, Lonza), PEG-20 glyceryl oleate (Tagat® O, Goldschmidt), and PEG-30 glyceryl oleate (Tagat® O2, Goldschmidt). Formulations of **rifalazil** according to the invention may include one or more of the polyethylene glycol glycerol fatty acid esters above.

DETD [0094] Alcohol-oil transesterification products may also be used as excipients for the formulation of **rifalazil.** Examples of commercially available alcohol-oil transesterification products include: PEG-3 castor oil (Nikkol CO-3, Nikko), PEG-5, 9, and 16 castor oil. . . derivatives of these vitamins, such as tocopheryl PEG 1000 succinate (TPGS, available from Eastman), are also suitable surfactants. Formulations of **rifalazil** according to the invention may

include one or more of the alcohol-oil transesterification products above.

DETD [0095] Polyglycerized fatty acids may also be used as excipients for the formulation of **rifalazil**. Examples of commercially available polyglycerized fatty acids include: polyglyceryl-2 stearate (Nikkol DGMS, Nikko), polyglyceryl-2 oleate (Nikkol DGMO, Nikko), polyglyceryl-2 isostearate. . . Nikko), polyglyceryl-101 decaoleate (Drewpol 10-10-O, Stepan), polyglyceryl-10 mono, dioleate (Caprol® PGE 860, ABITEC), and polyglyceryl polyricinoleate (Polymuls, Henkel). Formulations of **rifalazil** according to the invention may include one or more of the polyglycerized fatty acids above.

DETD [0096] In addition, propylene glycol fatty acid esters may be used as excipients for the formulation of **rifalazil**. Examples of commercially available propylene glycol fatty acid esters include: propylene glycol monocaprylate (Capryol 90, Gattefosse), propylene glycol monolaurate (Lauroglycol. . . distearate (Kessco® PGDS, Stepan), propylene glycol dicaprylate (Nikkol Sefsol 228, Nikko), and propylene glycol dicaprate (Nikkol PDD, Nikko). Formulations of **rifalazil** according to the invention may include one or more of the propylene glycol fatty acid esters above.

DETD [0097] Mixtures of propylene glycol esters and glycerol esters may also be used as excipients for the formulation of **rifalazil**. One preferred mixture is composed of the oleic acid esters of propylene glycol and glycerol (Arlacel 186). Examples of these surfactants include: oleic (ATMOS 300, ARLACEL 186, ICI), and stearic (ATMOS 150). Formulations of **rifalazil** according to the invention may include one or more of the mixtures of propylene glycol esters and glycerol esters above.

DETD [0098] Further, mono- and diglycerides may be used as excipients for the formulation of **rifalazil**. Examples of commercially available mono- and diglycerides include: monopalmitolein (C16:1) (Larodan), monoelaidin (C18:1) (Larodan), monocaproin (C6) (Larodan), monocaprylin (Larodan), monocaprin. . . 39/01, Gattefosse), dipalmitolein (C16:1) (Larodan), 1,2 and 1,3-diolein (C18:1) (Larodan), dielaidin (C18:1) (Larodan), and dilinolein (C 18:2) (Larodan). Formulations of **rifalazil** according to the invention may include one or more of the mono- and diglycerides above.

DETD [0099] Sterol and sterol derivatives may also be used as excipients for the formulation of **rifalazil**. Examples of commercially available sterol and sterol derivatives include: cholesterol, sitosterol, lanosterol, PEG-24 cholesterol ether (Solulan C-24, Amerchol), PEG-30 cholestanol. . . BPS-5, Nikko), PEG-10 soyasterol (Nikkol BPS-10, Nikko), PEG-20 soyasterol (Nikkol BPS-20, Nikko), and PEG-30 soyasterol (Nikkol BPS-30, Nikko). Formulations of **rifalazil** according to the invention may include one or more of the sterol and sterol derivatives above.

DETD [0100] Polyethylene glycol sorbitan fatty acid esters may also be used as excipients for the formulation of **rifalazil**. Examples of commercially available polyethylene glycol sorbitan fatty acid esters include: PEG-10 sorbitan laurate (Liposorb L-10, Lipo Chem.), PEG-20 sorbitan. . . Pharma), polysorbate 40 (Tween® 40, Pharma), polysorbate 60 (Tween® 60, Pharma), and PEG-6 sorbitol hexastearate (Nikkol GS-6, Nikko). Formulations of **rifalazil** according to the invention may include one or more of the polyethylene glycol sorbitan fatty acid esters above.

DETD [0101] In addition, polyethylene glycol alkyl ethers may be used as excipients for the formulation of **rifalazil**. Examples of commercially available polyethylene glycol alkyl ethers include: PEG-2 oleyl ether, oleth-2 (Brij 92/93, Atlas/ICI), PEG-3 oleyl ether, oleth-3. . . stearyl ether (Brij 76, ICI), PEG-20 stearyl ether (Brij

78, ICI), and PEG-100 stearyl ether (Brij 700, ICI). Formulations of **rifalazil** according to the invention may include one or more of the polyethylene glycol alkyl ethers above.

DETD [0102] Sugar esters may also be used as excipients for the formulation of **rifalazil.** Examples of commercially available sugar esters include: sucrose distearate (SUCRO ESTER 7, Gattefosse), sucrose distearate/monostearate (SUCRO ESTER 11, Gattefosse), sucrose. . . sucrose monostearate (Crodesta F-160, Croda), sucrose monopalmitate (SUCRO ESTER 15, Gattefosse), and sucrose monolaurate (Saccharose monolaurate 1695, Mitsubisbi-Kasei). Formulations of **rifalazil** according to the invention may include one or more of the sugar esters above. polyethylene glycol alkyl phenols are also useful as excipients for the formulation of **rifalazil.** Examples of commercially available polyethylene glycol alkyl phenols include: PEG-10-100 nonylphenol series (Triton X series, Rohm & Haas) and PEG-15-100 octylphenol ether series (Triton N-series, Rohm & Haas). Formulations of **rifalazil** according to the invention may include one or more of the polyethylene glycol alkyl phenols above.

DETD [0103] Polyoxyethylene-polyoxypropylene block copolymers may also be used as excipients for the formulation of **rifalazil.** These surfactants are available under various trade names, including one or more of Synperonic PE series (ICI), Pluronicg series (BASF),. . .

DETD . . . ranging from 1000 to 15000 daltons, and with ethylene oxide/propylene oxide ratios between 0.1 and 0.8 by weight. Formulations of **rifalazil** according to the invention may include one or more of the polyoxyethylene-polyoxypropylene block copolymers above.

DETD [0105] Polyoxyethylenes, such as PEG 300, PEG 400, and PEG 600, may be used as excipients for the formulation of **rifalazil.**

DETD [0106] Sorbitan fatty acid esters may also be used as excipients for the formulation of **rifalazil.** Examples of commercially sorbitan fatty acid esters include: sorbitan monolaurate (Span-20, Atlas/ICI), sorbitan monopalmitate (Span-40, Atlas/ICI), sorbitan monooleate (Span-80, Atlas/ICI),. . . sesquioleate (Arlacel-C, ICI), sorbitan tristearate (Span-65, Atlas/ICI), sorbitan monoisostearate (Crill 6, Croda), and sorbitan sesquistearate (Nikkol SS-15, Nikko). Formulations of **rifalazil** according to the invention may include one or more of the sorbitan fatty acid esters above.

DETD . . . IPM, Croda), isopropyl palmitate (Crodamol IPP, Croda), ethyl linoleate (Nikkol VF-E, Nikko), and isopropyl linoleate (Nikkol VF-IP, Nikko). Formulations of **rifalazil** according to the invention may include one or more of the lower alcohol fatty acid esters above.

DETD [0108] In addition, ionic surfactants may be used as excipients for the formulation of **rifalazil.** Examples of useful ionic surfactants include: sodium caproate, sodium caprylate, sodium caprate, sodium laurate, sodium myristate, sodium myristolate, sodium palmitate,. . . glyco cheno deoxycholate, sodium cholylsarcosinate, sodium N-methyl taurocholate, egg yolk phosphatides, hydrogenated soy lecithin, dimyristoyl lecithin, lecithin, hydroxylated lecithin, lysophosphatidylcholine, **cardiolipin**, sphingomyelin, phosphatidylcholine, phosphatidyl ethanolamine, phosphatidic acid, phosphatidyl glycerol, phosphatidyl serine, diethanolamine, phospholipids, polyoxyethylene-10 oleyl ether phosphate, esterification products of fatty. . . sodium salts, other cation counterions can also be used, such as, for example, alkali metal cations or ammonium. Formulations of **rifalazil** according to the invention may include one or more of the ionic surfactants above.

DETD . . . formulations of the invention are present in amounts such that the carrier forms a clear, or opalescent, aqueous dispersion of **rifalazil.** The relative amount of an excipient necessary for the preparation of the solutions described herein is readily determined by

observing the solubility of **rifalazil** in the solution. For example, the optical clarity of the aqueous dispersion can be measured using standard quantitative techniques for. . .

DETD . . . glucose. Alternatively, nanoparticulate formulations (e.g., biodegradable nanoparticles, solid lipid nanoparticles) may be used to prepare an intravenous dosage form of **rifalazil.** Other potentially useful intravenous delivery systems include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes.

DETD [0113] **Rifalazil** formulations and compositions described herein may also include a second therapeutic agent, including for example, another antibiotic, an anesthetic, an. . .

DETD [0114] Antibiotics that can be admixed with the intravenous **rifalazil** formulation include: aminoglycosides, such as amikacin, apramycin, arbekacin, ambermycins, butirosin, dibekacin, dihydrostreptomycin, fortimicin(s), fradiomycin, gentamicin, ispamicin, kanamycin, micronomicin, neomycin, neomycin. . .

DETD . . . goal of therapy (treatment or prophylaxis), the anticipated duration, and the severity of the infection or disease for which intravenous **rifalazil** is being administered. Additional considerations in dose selection include the type of infection, age of the patient (e.g., pediatric, adult,. . . Determining what concentrations to employ are within the skills of the pharmacist, medicinal chemist, or medical practitioner formulating the intravenous **rifalazil** in combination with other therapeutic agents.

DETD . . . the invention is that the intravenous dosage formulations provide clinicians with the ability to directly adjust the plasma levels of **rifalazil** to the point of therapeutic efficacy by controlling the dose and the schedule of drug administration. Adjusting the dose and. . .

DETD [0122] **Rifalazil** can be administered by intravenous infusion, wherein between 1 and 48 mg of **rifalazil** is administered over a period of 4 to 24 hours. Desirably, between 1 and 40 mg, 1 and 30 mg, 2 and 30 mg, 3 and 30 mg, or 4 and 25 mg of **rifalazil** is administered over a period of 4 to 24 hours, 8 to 24 hours, 15 to 24 hours, or 20. . . 19, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, or 50 mg of **rifalazil** is administered by intravenous infusion over a 2, 4, 5, 6, 7, 8, 9, 10, 12, 14, 20, 24, 48,. . .

DETD [0123] Alternatively, **rifalazil** can be administered by intravenous bolus followed by slow infustion. Desirably, a bolus injection of between 2 and 25 mg of **rifalazil** over a 10 to 60 minute period is followed by a slow infusion of 0.1 to 2 mg per hour. . .

DETD [0124] The intravenous administration of **rifalazil** may be repeated daily or every other day, for a period of two to fourteen days. The intravenous administration may. . .

DETD [0125] Adjusting the dose and schedule of drug administration as described herein, **rifalazil** can be intravenously administered at a rate that maintains a plasma concentration of **rifalazil** of between 2 and 100, 2 and 80, 2 and 60, 2 and 40, 2 and 30,2 and 20,2 and. . .

DETD [0126] Desirably, **rifalazil** is administered in a dosing regimen that maintains a plasma concentration of **rifalazil** of between 2 and 40 ng/mL for a period greater than 24 hours.

DETD [0134] Further, obligate intracellular protozoans can also be treated by intravenous administration of **rifalazil** as described herein. Obligate intracellular protozoans that may be treated by the methods of the invention include, for example, Brachiola. . .

DETD [0135] The **rifalazil** formulations described herein can further

be used to treat or prevent viral infections.

DETD . . . (MS), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), interstitial cystitis (IC), fibromyalgia (FM), autonomic nervous dysfunction (AND, neural-mediated hypotension); pyoderma **gangrenosum** (PG), chronic fatigue (CF) and chronic fatigue syndrome (CFS).

DETD . . . bowel disease, ulcerative colitis, and Crohn's disease and vascular inflammatory pathologies, such as, but not limited to, disseminated intravascular coagulation, **atherosclerosis**, and Kawasaki's pathology are also suitable for treatment by methods described herein. The invention can also be used to treat inflammatory diseases such as coronary **artery** disease, hypertension, **stroke**, asthma, chronic hepatitis, multiple sclerosis, peripheral neuropathy, chronic or recurrent sore throat, laryngitis, tracheobronchitis, chronic vascular headaches (including migraines, cluster. . .

DETD [0144] The compositions of the invention may be packaged together with instructions for the intravenous administration of a **rifalazil** . Typically, the instructions will also include the dosage and rate of administration. In some instances, instructions may be included on a label or on a package insert accompanying an intravenous pharmaceutical formulation containing **rifalazil.**

DETD . . . The method of the invention can be incorporated into a prepackaged therapeutic regimen designed to deliver a specific dose of **rifalazil** over a specific period of time to a human patient. For example, a sufficient amount of **rifalazil** can be administed as a "push" over ten to sixty minutes to produce a desired blood level and the remainder. . . to a total of 24 hours at such a rate that the blood level would remain constant. In this manner **rifalazil** may be intravenously administered every day, every other day, every third day for a period of up twelve days, or. . .

DETD [0146] The compositions can also be packaged as a concentrate including **rifalazil** and micelle-forming excipient. The concentrate optionally includes some water. For example, the concentrate can be less than 40%, 20%, 10%,. . . water by volume. The concentrate contains greater than 100 μg/mL, 1 mg/mL, 5 mg/mL, 10 mg/mL, or 20 mg/mL of **rifalazil.** Concentrates are formulated for intravenous adminstration by the addition of water, which may include other pharmaceutically acceptable excipients, such as buffer or saline, in an amount necessary to achieve the concentration of **rifalazil** to be administered.

DETD [0148] In order to determine its solubility, to a vial containing solid **rifalazil** was added a volume of aqueous test solution. The vial was capped and sonicated for about an hour and the. . . minute, sonicated for another 30 minutes, and centrifuged for 1 hour at 3500 RPM. The supernatent was separated from undissolved **rifalazil.** The concentration of **rifalazil** in the test solution was determined by UV-Vis absorbance using a suitable spectrophotometer. Using this method, the solubility of **rifalazil** was determined as a function of pH (see FIG. 1); in PEG 400-water, propylene glycol-water, and ethanol-water mixtures (see FIG.. . .

DETD Formulation of **Rifalazil** for Intravenous Administration

DETD . . . buffer (pH=7.6), 1.0% (v/v) PEG-35 castor oil, and 0.9% (w/v) NaCl was added from 2.5 mg to 25 mg of **rifalazil.** The solution was gently agitated until no undissolved solids remained.

DETD [0150] **Rifalazil** solutions containing the micelle-forming excipient PEG-35 castor oil, prepared as described in Example 2, and without a micelle-forming excipient (15% ethanol, phosphate buffer pH=7.6, 0.9% NaCl) were monitored for stability against the hydrolytic degradation of **rifalazil** at temperatures of 25° C.,

40° C., 50° C., and 60° C. (see FIGS. 7 and 8). The degradation was monitored for several days by HPLC for the disappearance of **rifalazil** or the appearance of des-acetyl **rifalazil**, the degradation product that results from the hydrolysis of **rifalazil**. The presence of a micelle-forming excipient inhibits the hydrolytic degradation of **rifalazil**, as shown in FIGS. 7 and 8.

DETD [0151] The MIC (minimum inhibitory concentration) of **rifalazil** against S. aureus was determined by the broth microdilution method. A vehicle prepared as described in Example 2 was diluted. . . .

DETD . . . CAMH broth to yield an inoculum suspension containing approximately 10.sup.6 CFU/ml. Aliquots of the inoculum suspension were added to the **rifalazil**-containing wells to yield a final concentration in the well of 1-8+10.sup.5 CFU/ml. The microtiter plates were incubated at 35-37° C.. . . .

DETD [0153] **Rifalazil** was evaluated in a murine model of bacterial infection in which female mice that weighed approximately 20 g were challenged. . . . from a log phase broth culture, sufficient in number to kill non-treated control mice within 24 to 48 hours. 20 **Rifalazil** was tested using the procedure described by Weiss et al., Antimicrobial Agents and Chemotherapy 43:460-464 (1999).

DETD [0154] **Rifalazil** was administered to mice 30 minutes after inoculation with bacteria, either by intravenous route, using the vehicle prepared as described. . . . three days following treatment. The MIC, intravenous ED.sub.50, and oral ED.sub.50 are provided in Table 1.

TABLE 1

Effective Dose of **Rifalazil** (μg/mL)

MIC	IV ED.sub.50	Oral ED.sub.50
0.015	0.053	0.098

CLM What is claimed is:

1. An aqueous solution of **rifalazil** suitable for intravenous administration to a human, wherein said solution has a **rifalazil** concentration of between 10 to 10,000 μg/mL.

2. The solution of claim 1, wherein said **rifalazil** concentration is between 50 and 10,000 μg/mL.

3. The solution of claim 2, wherein said **rifalazil** concentration is between 100 and 2,000 82 g/mL.

7. An aqueous composition for inhibiting the hydrolytic decomposition of **rifalazil** dissolved therein, said composition comprising **rifalazil**, water, and a micelle-forming excipient.

8. A method for inhibiting the hydrolytic decomposition of **rifalazil**, said method comprising formulating said **rifalazil** in an aqueous solution containing a micelle-forming excipient.

9. A method of treating a disease in a human, said method comprising administering **rifalazil** intravenously to said human in an amount effective to treat said disease.

10. The method of claim 9, wherein said administration of **rifalazil** comprises an intravenous infusion of between 1 and 48 mg of **rifalazil** to said human over a period of 4 to 24 hours.

11. The method of claim 10, wherein said administration of **rifalazil** comprises: (a) a bolus injection of between 2 and 25 mg of **rifalazil** over 10 to 60 minutes, and (b) following step (a), a slow infusion of between 0.1 and 2 mg per. . .
13. The method of claim 9, wherein said **rifalazil** is administered in an amount necessary to maintain a **rifalazil** concentration of between 2 and 100 ng/mL in the plasma of said human for a period greater than 5 hours.
. . .
14. The method of claim 13, wherein said **rifalazil** is administered in an amount necessary to maintain a **rifalazil** concentration of between 2 and 40 ng/mL in the plasma of said human for a period greater than 24 hours.
. . .
17. The method of claims 9, wherein said disease is selected from the group consisting of **atherosclerosis**, multiple sclerosis, rheumatoid arthritis, diabetes, Alzheimer's disease, asthma, cirrhosis of the liver, psoriasis, meningitis, cystic fibrosis, cancer, and osteoporosis.

18. The method of claim 9, wherein said **rifalazil** is administered for prophylaxis against an infection resulting from a surgical procedure or implantation of a prosthetic device.

. . . A method of treating an infection by multi-drug resistant bacteria in a human, said method comprising the intravenous administration of **rifalazil** to said human in an amount effective to treat said infection.

36. A method for treating or preventing the development of an **atherosclerosis**-associated disease in a human patient in need thereof, said method comprising the intravenous administration of **rifalazil** to said patient in an amount effective to treat or prevent the development of said **atherosclerosis**-associated disease in said patient.
44. The method of claim 36, wherein said **atherosclerosis** -associated disease is coronary **artery** disease, **myocardial** infarction, **angina** pectoris, **stroke** , **cerebral ischemia**, intermittent **claudication**, **gangrene**, mesenteric **ischemia**, temporal **arteritis**, or renal **artery** stenosis.

. . . 45. The method of claim 36, wherein, prior to administration of said compound, said patient is diagnosed as having said **atherosclerosis**-associated disease.

. . . protein in a human patient identified as having increased levels of C-reactive protein, said method comprising the intravenous administration of **rifalazil** to said patient in an amount effective to reduce the level of C-reactive protein.

. . . replication in macrophages or foam cells in a human patient in need thereof, said method comprising the intravenous administration of **rifalazil** to said patient in an amount effective to reduce Chlamydia pneumoniae replication in macrophages or foam cells in said patient.
. . .
. . . persistent Chlamydia pneumoniae infection in macrophages or foam cells in a human patient, said method comprising the intravenous

administration of **rifalazil** to said patient in an amount effective to treat said Chlamydia pneumoniae infection in macrophages or foam cells in said. . .

. . . infection of a bacterium having a multiplying form and a non-multiplying form, said method comprising administering to a patient (i) **rifalazil**; and (ii) a second antibiotic effective against the multiplying form of said bacterium, wherein said **rifalazil** is administered intravenously in an amount and for a duration effective to treat the non-multiplying form of said bacterium and. . .

. . . a duration to reduce the presence of said bacterium in said patient to less than about 10.sup.6 organisms/mL; and said **rifalazil** is then administered intravenously to said patient in an amount and for a duration effective to reduce the presence of. . .

. . . method of eradicating non-multiplying bacteria not eradicated in a patient following treatment with a first antibiotic, said method comprising administering **rifalazil** intravenously to said patient in an amount and for a duration effective to eradicate said non-multiplying bacteria in said patient.

. . .

. . . a bacterial infection caused by bacteria capable of establishing a non-multiplying form phase, said method comprising the step of administering **rifalazil** intravenously to said patient, wherein said administering is for a duration and in an amount effective to treat said patient.

. . .

55. The method of claim 54, wherein said inflammatory disease is selected from the group consisting of asthma, coronary **artery** disease, arthritis, conjunctivitis, lymphogranuloma venerum, cervicitis, and salpingitis.

58. The method of claim 53, wherein said chronic disease is **atherosclerosis.**

59. A method of treating the cryptic phase of a bacterial infection, said method comprising the step of administering **rifalazil** intravenously to a patient, wherein said administering is for a duration and in an amount effective to treat said cryptic. . .

60. A pharmaceutical formulation comprising **rifalazil** for intravenous administration, wherein said formulation is packaged with a label or package insert providing instructions for the use of. . .

61. A concentrate comprising **rifalazil** and a micelle-forming excipient, wherein said concentrate comprises less than 40% water by volume and greater than 100 μg/mL of **rifalazil.**

. . . concentrate of claim 61, wherein said concentrate comprises less than 5% water by volume and greater than 1 mg/mL of **rifalazil.**

L160 ANSWER 18 OF 21 USPATFULL on STN
ACCESSION NUMBER: 2004:19446 USPATFULL
TITLE: Metal complexes and formulations of rifamycin analogues and uses thereof
INVENTOR(S): **Michaelis, Arthur F.**, Devon, PA, UNITED STATES
Maulding, Hawkins V., Mendham, NJ, UNITED STATES
Sayada, Chalom, Luxembourg City, MA, UNITED STATES
Eisenstein, Barry, Chestnut Hill, MA, UNITED STATES

NUMBER	KIND	DATE

PATENT INFORMATION:	US 2004014750	A1	20040122
APPLICATION INFO.:	US 2002-318998	A1	20021212 (10)

PRIORITY INFORMATION:	NUMBER	DATE
	US 2001-341591P	20011213 (60)
	US 2002-382805P	20020523 (60)
	US 2002-385532P	20020603 (60)
	US 2002-406873P	20020829 (60)
	US 2002-412958P	20020923 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: CLARK & ELBING LLP, 101 FEDERAL STREET, BOSTON, MA, 02110
NUMBER OF CLAIMS: 157
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 2451
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention features compositions that include rifamycin analogues formulated with metal salts, metal complexes of rifamycin analogues, and methods for treating disease using these compositions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IN **Michaelis, Arthur F.**, Devon, PA, UNITED STATES
IN **Sayada, Chalom**, Luxembourg City, MA, UNITED STATES
SUMM [0038] The invention also features a method for treating or preventing the development of an **atherosclerosis**-associated disease in a patient by administering to the patient a metal complex or formulation of the invention in an amount effective to treat or prevent the development of the **atherosclerosis**-associated disease in the patient. The patient is typically diagnosed as having the **atherosclerosis**-associated disease (or being at increased risk of developing the disease) or as having macrophages or foam cells infected with C.. . .
SUMM . . . complex or formulation of the invention. The stent can be, e.g., a wire mesh tube used to hold open an **artery.** Stents are typically inserted following angioplasty.
SUMM . . . The chronic disease may be an inflammatory disease. Examples of inflammatory diseases include but are not limited to asthma, coronary **artery** disease, arthritis, conjunctivitis, lymphogranuloma venerum (LGV), cervicitis, and salpingitis. The chronic disease can also be an autoimmune disease (e.g., systemic. . .
SUMM [0094] By "**atherosclerosis**" is meant the progressive accumulation of smooth muscle cells, immune cells (e.g., lymphocytes, macrophages, or monocytes), lipid products (e.g., lipoproteins, or cholesterol), cellular waste products, calcium, or other substances within the inner lining of an **artery**, resulting in the narrowing or obstruction of the blood vessel and the development of **atherosclerosis**-associated diseases. **Atherosclerosis** is typically manifested within large and medium-sized **arteries** , and is often characterized by a state of chronic inflammation within the **arteries.**
SUMM [0095] By "**atherosclerosis**-associated disease" is meant any disorder that is caused by or is associated with **atherosclerosis** . Typically, **atherosclerosis** of the coronary **arteries** commonly causes coronary **artery** disease, **myocardial** infarction, coronary thrombosis, and **angina** pectoris. **Atherosclerosis** of the **arteries** supplying the central

nervous system frequently provokes **strokes** and transient **cerebral ischemia.** In the peripheral circulation, **atherosclerosis** causes intermittent **claudication** and **gangrene** and can jeopardize limb viability. **Atherosclerosis** of an **artery** of the splanchnic circulation can cause mesenteric **ischemia.** **Atherosclerosis** can also affect the kidneys directly (e.g., renal **artery** stenosis).

SUMM [0096] A patient who is being treated for an **atherosclerosis** -associated disease is one who a medical practitioner has diagnosed as having such a disease. Diagnosis may be by any suitable means. Methods for diagnosing **atherosclerosis** by measuring systemic inflammatory markers are described, for example, in U.S. Pat. No. 6,040,147, hereby incorporated by reference. Diagnosis and monitoring may employ an **electrocardiogram**, chest X-ray, **echocardiogram**, **cardiac** catheterization, ultrasound (for the measurement of vessel wall thickness), or measurement of blood levels of CPK, CPK-MB, myoglobin, troponin, homocysteine, or C-reactive protein. A patient in whom the development of an **atherosclerosis** -associated disease is being prevented is one who has not received such a diagnosis. One in the art will understand that these patients may have been subjected to the same tests (**electrocardiogram**, chest X-ray, etc.) or may have been identified, without examination, as one at high risk due to the presence of. . . prophylactic administration of a metal complex or formulation of the invention is considered to be preventing the development of an **atherosclerosis**-associated disease.

SUMM [0097] An **atherosclerosis**-associated disease has been treated or prevented when one or more tests of the disease (e.g., any of the those described. . . improved or the patient's risk reduced. In one example, a reduction in C-reactive protein to normal levels indicates that an **atherosclerosis**-associated disease has been treated or prevented.

SUMM . . . of C. pneumoniae. Any suitable method may be employed (e.g., determination of C. pneumoniae in blood monocytes or in the **atheroma** itself (e.g., in macrophages or foam cells present in the fatty streak), or detection of C. pneumoniae DNA, RNA, or. . .

SUMM . . . mononuclear cells (e.g., macrophages, lymphocytes, and plasma cells), tissue destruction, and fibrosis. Non-limiting examples of inflammatory disease include asthma, coronary **artery** disease, arthritis, conjunctivitis, lymphogranuloma venerum, and salpingitis.

DETD . . . animals with a pharmaceutically acceptable diluent, carrier, or excipient, in unit dosage form. Administration may be oral, topical, parenteral, intravenous, intra-**arterial**, subcutaneous, intramuscular, intracranial, intraorbital, ophthalmic, intraventricular, intracapsular, intraspinal, intracistemal, intraperitoneal, intranasal, aerosol, by suppositories, or by any other suitable route. . .

DETD [0152] In particular embodiments, a metal complex or formulation of the invention can be used to treat **atherosclerosis** or diseases associated therewith, sexually transmitted diseases caused, for example, by C. trachomatis or N. gonorrhoeae, otitis media and other. . .

DETD [0153] **Atherosclerosis** and Other Diseases Associated with Chlamydial Infection

DETD . . . several chronic disease syndromes of previously unknown etiology in humans. To date, these diseases include, but are not limited to, **atherosclerosis**, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, interstitial cystitis, fibromyalgia, autonomic nervous dysfunction (neural-mediated hypotension); pyoderma **gangrenosum**, and chronic fatigue syndrome.

DETD . . . of body fluids and/or tissues and several chronic disease

syndromes as described above, (ii) published evidence of an association between **atherosclerosis** and Chlamydia (Circulation 96:404-407, 1997), and (iii) an understanding of the impact the persistent infection established by the cryptic phase. . .

DETD . . . bowel disease, ulcerative colitis, and Crohn's disease and vascular inflammatory pathologies, such as, but not limited to, disseminated intravascular coagulation, **atherosclerosis**, and Kawasaki's pathology are also suitable for treatment by methods described herein. The invention can also be used to treat inflammatory diseases such as coronary **artery** disease, hypertension, **stroke**, asthma, chronic hepatitis, multiple sclerosis, peripheral neuropathy, chronic or recurrent sore throat, laryngitis, tracheobronchitis, chronic vascular headaches (including migraines, cluster. . .

DETD [0229] To a solution of 6.00 g (6.38 mmol) of of compound 8 (**rifalazil**) in 400 mL of methanol was added 0.808 g (6.38 mmol) of Iron (II) chloride. The mixture was stirred for. . . for six hours to obtain the resulting product (6.9 g). The solubility in water for the resulting ferrous complex of **rifalazil** is 86.4 mg/mL. UV/Vis: λ.sub.max=618.0 nm, 354.5 nm, 270.0 nm, 216.5 nm, 209.5 nm. ESI (+) MS: 996 (Fe-**rifalazil**+H.sup.+), 1030.5 (FeCl-**rifalazil**+H.sup.+).

CLM What is claimed is:

47. A method for treating or preventing the development of an **atherosclerosis**-associated disease in a patient in need thereof, said method comprising administering a composition of claim 28 to said patient in an amount effective to treat or prevent the development of said **atherosclerosis**-associated disease in said patient.

60. The method of claim 47, wherein said **atherosclerosis** -associated disease is coronary **artery** disease, **myocardial** infarction, **angina** pectoris, **stroke** , **cerebral ischemia**, intermittent **claudication**, **gangrene**, mesenteric **ischemia**, temporal **arteritis**, or renal **artery** stenosis.

. . . 61. The method of claim 47, wherein, prior to administration of said compound, said patient is diagnosed as having said **atherosclerosis**-associated disease.

132. The method of claim 131, wherein said inflammatory disease is selected from the group consisting of asthma, coronary **artery** disease, arthritis, conjunctivitis, lymphogranuloma venerum, cervicitis, and salpingitis.

L160 ANSWER 19 OF 21 USPATFULL on STN
ACCESSION NUMBER: 2004:19445 USPATFULL
TITLE: Sulfhydryl rifamycins and uses thereof
INVENTOR(S): **Michaelis, Arthur F.**, Devon, PA, UNITED STATES
Maulding, Hawkins V., Mendham, NJ, UNITED STATES
Sayada, Chalom, Luxembourg City, LUXEMBOURG
Eisenstein, Barry, Chestnut Hill, MA, UNITED STATES
Geiss, William B., Athens, NY, UNITED STATES
Raker, Joseph, Delmar, NY, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004014749	A1	20040122

APPLICATION INFO.: US 2002-318582 A1 20021212 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-341130P	20011213 (60)
	US 2002-382805P	20020523 (60)
	US 2002-385532P	20020603 (60)
	US 2002-406873P	20020829 (60)
	US 2002-412958P	20020923 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: CLARK & ELBING LLP, 101 FEDERAL STREET, BOSTON, MA, 02110
NUMBER OF CLAIMS: 163
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 2259
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention features sulfhydryl rifamycin compositions, methods of making these compositions, and methods for treating disease using these compositions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IN **Michaelis, Arthur F.**, Devon, PA, UNITED STATES
IN **Sayada, Chalom**, Luxembourg City, LUXEMBOURG

L160 ANSWER 20 OF 21 USPATFULL on STN
ACCESSION NUMBER: 2004:2054 USPATFULL
TITLE: Hybrid oligonucleotide primers for amplification of DNA and uses thereof
INVENTOR(S): **Sayada, Chalom**, Luxembourg City, LUXEMBOURG
Denamur, Erick, Paris, FRANCE
Magnant, Gary, Topsfield, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004002074	A1	20040101
APPLICATION INFO.:	US 2002-300369	A1	20021120 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-331915P	20011120 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: CLARK & ELBING LLP, 101 FEDERAL STREET, BOSTON, MA, 02110
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 871
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides compositions and methods for the determination of the presence of specific microorganisms in a sample using the amplification of DNA. The invention further provides compositions and methods that provide an internal standard for the validation of the amplification of DNA. The invention is based on the use of hybrid oligonucleotides that have two domains that are specific for two genetically distinct regions of DNA, e.g., in two genetically distinct microorganisms.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IN **Sayada, Chalom**, Luxembourg City, LUXEMBOURG
IN **Magnant, Gary**, Topsfield, MA, UNITED STATES

L160 ANSWER 21 OF 21 USPATFULL on STN
ACCESSION NUMBER: 2003:335387 USPATFULL
TITLE: Methods of treating bacterial infections and diseases associated therewith
INVENTOR(S): **Sayada, Chalom B.**, Luxembourg City, LUXEMBOURG

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003236265	A1	20031225
APPLICATION INFO.:	US 2003-443351	A1	20030522 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-382805P	20020523 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: CLARK & ELBING LLP, 101 FEDERAL STREET, BOSTON, MA, 02110
NUMBER OF CLAIMS: 30
EXEMPLARY CLAIM: 1
LINE COUNT: 814
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention features methods and compositions for treating non-multiplying forms of bacterial infections.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IN **Sayada, Chalom B.**, Luxembourg City, LUXEMBOURG
SUMM . . . selected from the group consisting of methyl, ethyl, iso-propyl, n-propyl, iso-butyl, (S)-sec-butyl, and (R)-sec-butyl. One particularly preferred rifamycin antibiotic is **rifalazil.**
SUMM . . . and for a duration sufficient to complete the treatment of the patient. A typical treatment, particularly if the antibiotic is **rifalazil**, will comprise administration of between 0.1 g and 1 g for 1 to 3, 7, or 15 days, although longer. . .
SUMM . . . used to treat diseases associated with bacterial infection. For example, bacterial infections can produce inflammation, resulting in the pathogenesis of **atherosclerosis**, multiple sclerosis, rheumatoid arthritis, diabetes, Alzheimer's disease, asthma, cirrhosis of the liver, psoriasis, meningitis, cystic fibrosis, cancer, or osteoporosis. Accordingly,. . .
SUMM . . . mononuclear cells (e.g., macrophages, lymphocytes, and plasma cells), tissue destruction, and fibrosis. Non-limiting examples of inflammatory disease include asthma, coronary **artery** disease, arthritis, conjunctivitis, lymphogranuloma venerum, and salpingitis.
DETD . . . incorporated by reference. In preferred embodiments, the rifamycin antibiotic employed in the methods and compositions of the present invention is **rifalazil** (**ABI1648**), ABI1657, or ABI1131. The specific chemical formula of **rifalazil** is that of formula II wherein R is a hydrogen atom; R.sup.1 is an acetyl group; R.sup.2 is a hydroxyl. . .
DETD . . . (MS), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), interstitial cystitis (IC), fibromyalgia (FM), autonomic nervous dysfunction (AND, neural-mediated hypotension); pyoderma **gangrenosum** (PG), chronic fatigue (CF) and chronic fatigue syndrome (CFS).

DETD . . . bowel disease, ulcerative colitis, and Crohn's disease and vascular inflammatory pathologies, such as, but not limited to, disseminated intravascular coagulation, **atherosclerosis**, and Kawasaki's pathology are also suitable for treatment by methods described herein. The invention can also be used to treat inflammatory diseases such as coronary **artery** disease, hypertension, **stroke**, asthma, chronic hepatitis, multiple sclerosis, peripheral neuropathy, chronic or recurrent sore throat, laryngitis, tracheobronchitis, chronic vascular headaches (including migraines, cluster. . .

CLM What is claimed is:

9. The method of claim 1, wherein said rifamycin antibiotic is **rifalazil.**

10. The method of claim 9, wherein said **rifalazil** is administered orally.

11. The method of claim 9, wherein said **rifalazil** is administered intravenously.

15. The method of claim 13, wherein said rifamycin antibiotic is **rifalazil.**

16. The method of claim 15, wherein said **rifalazil** is administered orally.

17. The method of claim 15, wherein said **rifalazil** is administered intravenously.

20. The composition of claim 17, wherein said rifamycin antibiotic is **rifalazil.**

23. The method of claim 22, wherein said inflammatory disease is selected from the group consisting of asthma, coronary **artery** disease, arthritis, conjunctivitis, lymphogranuloma venerum, cervicitis, and salpingitis.

26. The method of claim 21, wherein said chronic disease is **atherosclerosis.**

27. The method of claim 21, wherein said rifamycin antibiotic is **rifalazil.**

29. The method of claim 28, wherein said rifamycin antibiotic is **rifalazil.**

TEXT SEARCH

=> □

```
=> file hcaplus
FILE 'HCAPLUS' ENTERED AT 12:00:49 ON 06 MAR 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)
```



```
FILE COVERS 1907 - 6 Mar 2006  VOL 144 ISS 11
FILE LAST UPDATED: 5 Mar 2006  (20060305/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.
'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> d que nos L59

L3              STR
L5            1 SEA FILE=REGISTRY FAM FUL L3
L47          83 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5 (L) (THU OR BAC OR PAC OR
                PKT OR DMA)/RL
L48       44638 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ATHEROSCLER?/OBI OR ATHEROGEN?
                /OBI OR ATHEROM?/OBI  OR ARTERIOSCLER?/OBI
L49       35764 SEA FILE=HCAPLUS ABB=ON  PLU=ON  CORONAR?/OBI
L50             QUE  ABB=ON  PLU=ON  MYOCARD?/OBI OR CARDIO?/OBI
L51             QUE  ABB=ON  PLU=ON  ANGINA/OBI OR ANGOR PECTORIS/OBI OR
                STENOCARD?/OBI
L52             QUE  ABB=ON  PLU=ON  APOPLEX?/OBI OR STROKE/OBI OR CEREBR
                OVASC?/OBI
L53             QUE  ABB=ON  PLU=ON  (CEREBR?/OBI OR BRAIN?/OBI) (2A) (IS
                CHEM?/OBI OR ISCHAEM?/OBI)
L54             QUE  ABB=ON  PLU=ON  INTERMITT?/OBI (2A) CLAUDICAT?/OBI
L55             QUE  ABB=ON  PLU=ON  GANGREN?/OBI
L56             QUE  ABB=ON  PLU=ON  MESENTER?/OBI
L57             QUE  ABB=ON  PLU=ON  ARTERITIS/OBI OR AORTIT?/OBI OR HORT
                ON?/OBI
L58             QUE  ABB=ON  PLU=ON  RENAL ARTER?/OBI (2A) (OBSTRUCT?/OBI
                 OR STENO?/OBI)
L59           7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L47 AND (L48 OR L49 OR L50 OR
                L51 OR L52 OR L53 OR L54 OR L55 OR L56 OR L57 OR L58)


=> d que nos L60

L3              STR
L5            1 SEA FILE=REGISTRY FAM FUL L3
```

```
L48       44638 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ATHEROSCLER?/OBI OR ATHEROGEN?
                /OBI OR ATHEROM?/OBI  OR ARTERIOSCLER?/OBI
L49       35764 SEA FILE=HCAPLUS ABB=ON  PLU=ON  CORONAR?/OBI
L50             QUE  ABB=ON  PLU=ON  MYOCARD?/OBI OR CARDIO?/OBI
L51             QUE  ABB=ON  PLU=ON  ANGINA/OBI OR ANGOR PECTORIS/OBI OR
                STENOCARD?/OBI
L52             QUE  ABB=ON  PLU=ON  APOPLEX?/OBI OR STROKE/OBI OR CEREBR
                OVASC?/OBI
L53             QUE  ABB=ON  PLU=ON  (CEREBR?/OBI OR BRAIN?/OBI) (2A) (IS
                CHEM?/OBI OR ISCHAEM?/OBI)
L54             QUE  ABB=ON  PLU=ON  INTERMITT?/OBI (2A) CLAUDICAT?/OBI
L55             QUE  ABB=ON  PLU=ON  GANGREN?/OBI
L56             QUE  ABB=ON  PLU=ON  MESENTER?/OBI
L57             QUE  ABB=ON  PLU=ON  ARTERITIS/OBI OR AORTIT?/OBI OR HORT
                ON?/OBI
L58             QUE  ABB=ON  PLU=ON  RENAL ARTER?/OBI (2A) (OBSTRUCT?/OBI
                 OR STENO?/OBI)
L60             8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5 AND (L48 OR L49 OR L50 OR
                L51 OR L52 OR L53 OR L54 OR L55 OR L56 OR L57 OR L58)


=> d que nos L72

L3              STR
L5              1 SEA FILE=REGISTRY FAM FUL L3
L47            83 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5 (L) (THU OR BAC OR PAC OR
                PKT OR DMA)/RL
L61             QUE  ABB=ON  PLU=ON  (?MYOCARD? OR ?CARDIO?)/BI
L62             QUE  ABB=ON  PLU=ON  (?ATHEROSCLER? OR ?ATHEROGEN? OR ?AT
                HEROM?  OR ?ARTERIOSCLER?)/BI
L63             QUE  ABB=ON  PLU=ON  ?CORON?/BI
L64             QUE  ABB=ON  PLU=ON  (?ANGINA OR ANGOR PECTORIS OR ?STENO
                CARD?)/BI
L65             QUE  ABB=ON  PLU=ON  (?APOPLEX? OR ?STROKE? OR ?CEREBROVA
                SC?)/BI
L66       20307 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ((CEREBR? OR BRAIN?) (2A)
                (ISCHEM? OR ISCHAEM?))/BI
L67         549 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (INTERMITT? (2A) CLAUDICAT?)/B
                I
L68             QUE  ABB=ON  PLU=ON  ?GANGREN?/BI
L69             QUE  ABB=ON  PLU=ON  ?MESENTER?/BI
L70             QUE  ABB=ON  PLU=ON  (?ARTERITIS OR ?AORTIT? OR HORTON?)/
                BI
L71             QUE  ABB=ON  PLU=ON  (?RENAL ARTER? (2A) (OBSTRUCT? OR ST
                ENO?))/BI
L72             8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L61 OR L62 OR L63 OR L64 OR
                L65 OR L66 OR L67 OR L68 OR L69 OR L70 OR L71) AND (L47 OR L5)


=> d que nos L79

L3              STR
L5              1 SEA FILE=REGISTRY FAM FUL L3
L47            83 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5 (L) (THU OR BAC OR PAC OR
                PKT OR DMA)/RL
L48       44638 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ATHEROSCLER?/OBI OR ATHEROGEN?
                /OBI OR ATHEROM?/OBI  OR ARTERIOSCLER?/OBI
L49       35764 SEA FILE=HCAPLUS ABB=ON  PLU=ON  CORONAR?/OBI
L50             QUE  ABB=ON  PLU=ON  MYOCARD?/OBI OR CARDIO?/OBI
L51             QUE  ABB=ON  PLU=ON  ANGINA/OBI OR ANGOR PECTORIS/OBI OR
```

```
               STENOCARD?/OBI
L52            QUE  ABB=ON  PLU=ON  APOPLEX?/OBI OR STROKE/OBI OR CEREBR
               OVASC?/OBI
L53            QUE  ABB=ON  PLU=ON  (CEREBR?/OBI OR BRAIN?/OBI) (2A) (IS
               CHEM?/OBI OR ISCHAEM?/OBI)
L54            QUE  ABB=ON  PLU=ON  INTERMITT?/OBI (2A) CLAUDICAT?/OBI
L55            QUE  ABB=ON  PLU=ON  GANGREN?/OBI
L56            QUE  ABB=ON  PLU=ON  MESENTER?/OBI
L57            QUE  ABB=ON  PLU=ON  ARTERITIS/OBI OR AORTIT?/OBI OR HORT
               ON?/OBI
L58            QUE  ABB=ON  PLU=ON  RENAL ARTER?/OBI (2A) (OBSTRUCT?/OBI
                OR STENO?/OBI)
L59          7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L47 AND (L48 OR L49 OR L50 OR
               L51 OR L52 OR L53 OR L54 OR L55 OR L56 OR L57 OR L58)
L60          8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5 AND (L48 OR L49 OR L50 OR
               L51 OR L52 OR L53 OR L54 OR L55 OR L56 OR L57 OR L58)
L61            QUE  ABB=ON  PLU=ON  (?MYOCARD? OR ?CARDIO?)/BI
L62            QUE  ABB=ON  PLU=ON  (?ATHEROSCLER? OR ?ATHEROGEN? OR ?AT
               HEROM?  OR ?ARTERIOSCLER?)/BI
L63            QUE  ABB=ON  PLU=ON  ?CORON?/BI
L64            QUE  ABB=ON  PLU=ON  (?ANGINA OR ANGOR PECTORIS OR ?STENO
               CARD?)/BI
L65            QUE  ABB=ON  PLU=ON  (?APOPLEX? OR ?STROKE? OR ?CEREBROVA
               SC?)/BI
L66      20307 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ((CEREBR? OR BRAIN?) (2A)
               (ISCHEM? OR ISCHAEM?))/BI
L67        549 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (INTERMITT? (2A) CLAUDICAT?)/B
               I
L68            QUE  ABB=ON  PLU=ON  ?GANGREN?/BI
L69            QUE  ABB=ON  PLU=ON  ?MESENTER?/BI
L70            QUE  ABB=ON  PLU=ON  (?ARTERITIS OR ?AORTIT? OR HORTON?)/
               BI
L71            QUE  ABB=ON  PLU=ON  (?RENAL ARTER? (2A) (OBSTRUCT? OR ST
               ENO?))/BI
L72          8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L61 OR L62 OR L63 OR L64 OR
               L65 OR L66 OR L67 OR L68 OR L69 OR L70 OR L71) AND (L47 OR L5)
L73            QUE  ABB=ON  PLU=ON  ?INFLAMM?/BI
L74            QUE  ABB=ON  PLU=ON  (?ANTIBACT? OR ?ANTI BACT?)/BI
L75            QUE  ABB=ON  PLU=ON  PLATELET/BI
L76            QUE  ABB=ON  PLU=ON  ?COAGUL?/BI
L77            QUE  ABB=ON  PLU=ON  ?ANTIPYRET?/BI
L78            QUE  ABB=ON  PLU=ON  HYPOLEMIC AGENTS+NT/CT
L79          7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L59 OR L60 OR L72) AND (L73
               OR L74 OR L75 OR L76 OR L77 OR L78)


=> d que nos L81

L3             STR
L5           1 SEA FILE=REGISTRY FAM FUL L3
L47         83 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5 (L) (THU OR BAC OR PAC OR
               PKT OR DMA)/RL
L48      44638 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ATHEROSCLER?/OBI OR ATHEROGEN?
               /OBI OR ATHEROM?/OBI  OR ARTERIOSCLER?/OBI
L49      35764 SEA FILE=HCAPLUS ABB=ON  PLU=ON  CORONAR?/OBI
L50            QUE  ABB=ON  PLU=ON  MYOCARD?/OBI OR CARDIO?/OBI
L51            QUE  ABB=ON  PLU=ON  ANGINA/OBI OR ANGOR PECTORIS/OBI OR
               STENOCARD?/OBI
L52            QUE  ABB=ON  PLU=ON  APOPLEX?/OBI OR STROKE/OBI OR CEREBR
               OVASC?/OBI
```

```
L53             QUE  ABB=ON  PLU=ON  (CEREBR?/OBI OR BRAIN?/OBI) (2A) (IS
                CHEM?/OBI OR ISCHAEM?/OBI)
L54             QUE  ABB=ON  PLU=ON  INTERMITT?/OBI (2A) CLAUDICAT?/OBI
L55             QUE  ABB=ON  PLU=ON  GANGREN?/OBI
L56             QUE  ABB=ON  PLU=ON  MESENTER?/OBI
L57             QUE  ABB=ON  PLU=ON  ARTERITIS/OBI OR AORTIT?/OBI OR HORT
                ON?/OBI
L58             QUE  ABB=ON  PLU=ON  RENAL ARTER?/OBI (2A) (OBSTRUCT?/OBI
                 OR STENO?/OBI)
L59           7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L47 AND (L48 OR L49 OR L50 OR
                L51 OR L52 OR L53 OR L54 OR L55 OR L56 OR L57 OR L58)
L60           8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5 AND (L48 OR L49 OR L50 OR
                L51 OR L52 OR L53 OR L54 OR L55 OR L56 OR L57 OR L58)
L61             QUE  ABB=ON  PLU=ON  (?MYOCARD? OR ?CARDIO?)/BI
L62             QUE  ABB=ON  PLU=ON  (?ATHEROSCLER? OR ?ATHEROGEN? OR ?AT
                HEROM?  OR ?ARTERIOSCLER?)/BI
L63             QUE  ABB=ON  PLU=ON  ?CORON?/BI
L64             QUE  ABB=ON  PLU=ON  (?ANGINA OR ANGOR PECTORIS OR ?STENO
                CARD?)/BI
L65             QUE  ABB=ON  PLU=ON  (?APOPLEX? OR ?STROKE? OR ?CEREBROVA
                SC?)/BI
L66       20307 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ((CEREBR? OR BRAIN?) (2A)
                (ISCHEM? OR ISCHAEM?))/BI
L67         549 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (INTERMITT? (2A) CLAUDICAT?)/B
                I
L68             QUE  ABB=ON  PLU=ON  ?GANGREN?/BI
L69             QUE  ABB=ON  PLU=ON  ?MESENTER?/BI
L70             QUE  ABB=ON  PLU=ON  (?ARTERITIS OR ?AORTIT? OR HORTON?)/
                BI
L71             QUE  ABB=ON  PLU=ON  (?RENAL ARTER? (2A) (OBSTRUCT? OR ST
                ENO?))/BI
L72           8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L61 OR L62 OR L63 OR L64 OR
                L65 OR L66 OR L67 OR L68 OR L69 OR L70 OR L71) AND (L47 OR L5)
L80       15159 SEA FILE=HCAPLUS ABB=ON  PLU=ON  HYPOLIPEMIC AGENTS+NT/CT
L81           4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L59 OR L60 OR L72) AND L80


=> d que nos L130

L130          7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (RIFALAZIL AND (ARTER? OR
                ATHERO? OR ?ISCHEM?))/BI


=> s (L59-L60 or L72 or L79 or L81 or L130) not L155

L161          2 ((L59 OR L60) OR L72 OR L79 OR L81 OR L130) NOT L155

=> file medline

FILE 'MEDLINE' ENTERED AT 12:00:54 ON 06 MAR 2006

 FILE LAST UPDATED: 4 MAR 2006 (20060304/UP).  FILE COVERS 1950 TO DATE.

 On December 11, 2005, the 2006 MeSH terms were loaded.

 The MEDLINE reload for 2006 is now (26 Feb.) available.  For details
 on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
 See also:

    http://www.nlm.nih.gov/mesh/
```

printed with author search

http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

OLDMEDLINE is covered back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2006 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d que nos L94

```
L3              STR
L5              1 SEA FILE=REGISTRY FAM FUL L3
L17            92 SEA FILE=MEDLINE ABB=ON  PLU=ON  L5
L18           122 SEA FILE=MEDLINE ABB=ON  PLU=ON  RIFALAZIL OR ABI 1648 OR
                  ABI1648 OR KRM1648 OR KRM 1648
L83         81311 SEA FILE=MEDLINE ABB=ON  PLU=ON  ARTERIOSCLEROSIS+NT/CT
L84        266695 SEA FILE=MEDLINE ABB=ON  PLU=ON  ?CORONAR?
L85        106755 SEA FILE=MEDLINE ABB=ON  PLU=ON  MYOCARDIAL INFARCTION+NT/CT
L86         32890 SEA FILE=MEDLINE ABB=ON  PLU=ON  ANGINA PECTORIS+NT/CT
L87         35194 SEA FILE=MEDLINE ABB=ON  PLU=ON  CEREBROVASCULAR ACCIDENT+NT/CT

L88         36889 SEA FILE=MEDLINE ABB=ON  PLU=ON  BRAIN ISCHEMIA+NT/CT
L89          6289 SEA FILE=MEDLINE ABB=ON  PLU=ON  INTERMITT? (2A) CLAUDICAT?
L90          6320 SEA FILE=MEDLINE ABB=ON  PLU=ON  GANGRENE/CT
L91         40700 SEA FILE=MEDLINE ABB=ON  PLU=ON  MESENTER?
L92         20102 SEA FILE=MEDLINE ABB=ON  PLU=ON  ?ARTERIT? OR ?AORTIT? OR
                  HORTON?
L93          7970 SEA FILE=MEDLINE ABB=ON  PLU=ON  RENAL ARTERY OBSTRUCTION/CT
L94             0 SEA FILE=MEDLINE ABB=ON  PLU=ON  (L17 OR L18) AND (L83 OR L84
                  OR L85 OR L86 OR L87 OR L88 OR L89 OR L90 OR L91 OR L92 OR
                  L93)
```

=> d que nos L98

```
L3              STR
L5              1 SEA FILE=REGISTRY FAM FUL L3
L17            92 SEA FILE=MEDLINE ABB=ON  PLU=ON  L5
L18           122 SEA FILE=MEDLINE ABB=ON  PLU=ON  RIFALAZIL OR ABI 1648 OR
                  ABI1648 OR KRM1648 OR KRM 1648
L97               QUE  ABB=ON  PLU=ON  ?HEART? OR ?CARDIO? OR ?CEREBR? OR ?
                  VASCUL? OR ?NECROS?
L98             3 SEA FILE=MEDLINE ABB=ON  PLU=ON  L97 AND (L17 OR L18)
```

=> s (L94 or L98) not L156

L162 3 (L94 OR L98) NOT L156 printed with author search

=> file embase

FILE 'EMBASE' ENTERED AT 12:00:57 ON 06 MAR 2006

FILE COVERS 1974 TO 3 Mar 2006 (20060303/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> d que nos L117

L3              STR
L5            1 SEA FILE=REGISTRY FAM FUL L3
L34         191 SEA FILE=EMBASE ABB=ON  PLU=ON  L5
L35         193 SEA FILE=EMBASE ABB=ON  PLU=ON  RIFALAZIL OR ABI 1648 OR
                ABI1648 OR KRM1648 OR KRM 1648
L100        198 SEA FILE=EMBASE ABB=ON  PLU=ON  (L34 OR L35)
L101      76713 SEA FILE=EMBASE ABB=ON  PLU=ON  ARTERIOSCLEROSIS+NT/CT
L102     204748 SEA FILE=EMBASE ABB=ON  PLU=ON  ?CORONAR?
L103          0 SEA FILE=EMBASE ABB=ON  PLU=ON  MYOCARDIAL INFARCTION+NT/CT
L104    1084849 SEA FILE=EMBASE ABB=ON  PLU=ON  ?HEART? OR ?CARDIO? OR
                ?CARDIAC? OR ?CORONAR? OR ?INFARCT?
L105     101601 SEA FILE=EMBASE ABB=ON  PLU=ON  HEART INFARCTION+NT/CT
L106      35812 SEA FILE=EMBASE ABB=ON  PLU=ON  ANGINA PECTORIS+NT/CT
L107      43618 SEA FILE=EMBASE ABB=ON  PLU=ON  ANGINA?
L108     157618 SEA FILE=EMBASE ABB=ON  PLU=ON  CEREBROVASCULAR ACCIDENT+ALL/CT

L109      35653 SEA FILE=EMBASE ABB=ON  PLU=ON  BRAIN ISCHEMIA+NT/CT
L110       3928 SEA FILE=EMBASE ABB=ON  PLU=ON  INTERMITTENT CLAUDICATION+NT/CT

L111     180358 SEA FILE=EMBASE ABB=ON  PLU=ON  GANGREN? OR NECROS?
L112       8956 SEA FILE=EMBASE ABB=ON  PLU=ON  GANGREN?
L113      31453 SEA FILE=EMBASE ABB=ON  PLU=ON  MESENTER?
L114      13311 SEA FILE=EMBASE ABB=ON  PLU=ON  ?ARTERIT? OR ?AORTIT? OR
                HORTON?
L115       5423 SEA FILE=EMBASE ABB=ON  PLU=ON  KIDNEY ARTERY STENOSIS/CT
L117         16 SEA FILE=EMBASE ABB=ON  PLU=ON  L100 AND ((L101 OR L102 OR
                L103 OR L104 OR L105 OR L106 OR L107 OR L108 OR L109 OR L110
                OR L111 OR L112 OR L113 OR L114 OR L115))


=> d que nos L120

L3              STR
L5            1 SEA FILE=REGISTRY FAM FUL L3
L34         191 SEA FILE=EMBASE ABB=ON  PLU=ON  L5
L35         193 SEA FILE=EMBASE ABB=ON  PLU=ON  RIFALAZIL OR ABI 1648 OR
                ABI1648 OR KRM1648 OR KRM 1648
L100        198 SEA FILE=EMBASE ABB=ON  PLU=ON  (L34 OR L35)
L119      89144 SEA FILE=EMBASE ABB=ON  PLU=ON  ?ATHERO?
L120          2 SEA FILE=EMBASE ABB=ON  PLU=ON  L100 AND L119


=> s (L117 or L120) not L157

L163         16 (L117 OR L120) NOT L157

=> file biosis

FILE 'BIOSIS' ENTERED AT 12:01:00 ON 06 MAR 2006
Copyright (c) 2006 The Thomson Corporation

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
```

printed with author search

FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 1 March 2006 (20060301/ED)

=> d que nos L123

```
L3              STR
L5            1 SEA FILE=REGISTRY FAM FUL L3
L37         126 SEA FILE=BIOSIS ABB=ON  PLU=ON  L5
L38         138 SEA FILE=BIOSIS ABB=ON  PLU=ON  RIFALAZIL OR ABI 1648 OR
                ABI1648 OR KRM1648 OR KRM 1648
L121            QUE  ABB=ON  PLU=ON  ?ATHERO? OR ?ARTER? OR ?CORONAR? OR
                ?CARDIO? OR ?CARDIAC? OR ?ISCHEM? OR STROKE? OR ?ISCHAEM?
                 OR ?BRAIN? OR ?CEREBR?
L122        138 SEA FILE=BIOSIS ABB=ON  PLU=ON  (L37 OR L38)
L123          2 SEA FILE=BIOSIS ABB=ON  PLU=ON  L122 AND L121
```

=> d que nos L125

```
L3              STR
L5            1 SEA FILE=REGISTRY FAM FUL L3
L37         126 SEA FILE=BIOSIS ABB=ON  PLU=ON  L5
L38         138 SEA FILE=BIOSIS ABB=ON  PLU=ON  RIFALAZIL OR ABI 1648 OR
                ABI1648 OR KRM1648 OR KRM 1648
L122        138 SEA FILE=BIOSIS ABB=ON  PLU=ON  (L37 OR L38)
L124            QUE  ABB=ON  PLU=ON  ?HEART? OR ?CARDIAL OR ANGINA? OR ?C
                LAUDIC? OR ?GANGREN? OR ?NECROS? OR ?MESENT?
L125          5 SEA FILE=BIOSIS ABB=ON  PLU=ON  L122 AND L124
```

=> d que nos L127

```
L3              STR
L5            1 SEA FILE=REGISTRY FAM FUL L3
L37         126 SEA FILE=BIOSIS ABB=ON  PLU=ON  L5
L38         138 SEA FILE=BIOSIS ABB=ON  PLU=ON  RIFALAZIL OR ABI 1648 OR
                ABI1648 OR KRM1648 OR KRM 1648
L122        138 SEA FILE=BIOSIS ABB=ON  PLU=ON  (L37 OR L38)
L126            QUE  ABB=ON  PLU=ON  ?ARTERIT? OR ?AORTIT? OR HORTON?
L127          0 SEA FILE=BIOSIS ABB=ON  PLU=ON  L122 AND L126
```

=> s (L123 or L125 or L127) not L158

L164 7 (L123 OR L125 OR L127) NOT L158 → printed with author search

=> file uspatfull

```
FILE 'USPATFULL' ENTERED AT 12:01:04 ON 06 MAR 2006
CA INDEXING COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 2 Mar 2006 (20060302/PD)
FILE LAST UPDATED: 2 Mar 2006 (20060302/ED)
HIGHEST GRANTED PATENT NUMBER: US7007305
HIGHEST APPLICATION PUBLICATION NUMBER: US2006048257
CA INDEXING IS CURRENT THROUGH 28 Feb 2006 (20060228/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 2 Mar 2006 (20060302/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Dec 2005
```

USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Dec 2005

```
=> d que nos L135

L3              STR
L5            1 SEA FILE=REGISTRY FAM FUL L3
L132         21 SEA FILE=USPATFULL ABB=ON  PLU=ON  L5
L133         38 SEA FILE=USPATFULL ABB=ON  PLU=ON  RIFALAZIL OR ABI 1648 OR
                ABI1648 OR KRM1648 OR KRM 1648
L134     303236 SEA FILE=USPATFULL ABB=ON  PLU=ON  ?ARTER? OR ?ATHERO?
L135         13 SEA FILE=USPATFULL ABB=ON  PLU=ON  (L132 OR L133) AND L134


=> d que nos L151

L3              STR
L5            1 SEA FILE=REGISTRY FAM FUL L3
L132         21 SEA FILE=USPATFULL ABB=ON  PLU=ON  L5
L133         38 SEA FILE=USPATFULL ABB=ON  PLU=ON  RIFALAZIL OR ABI 1648 OR
                ABI1648 OR KRM1648 OR KRM 1648
L146            QUE  ABB=ON  PLU=ON  ?HEART? OR ?CARDIO? OR ?CARDIA? OR ?
                ANGINA? OR STROKE? OR ?CEREBR? OR ?BRAIN? OR ?CLAUDIC? OR
                 GANGREN? OR ?ISCHEM? OR ?ISCHAEM?
L151          7 SEA FILE=USPATFULL ABB=ON  PLU=ON  (L132 OR L133) (P) L146


=> d que nos L147

L3              STR
L5            1 SEA FILE=REGISTRY FAM FUL L3
L132         21 SEA FILE=USPATFULL ABB=ON  PLU=ON  L5
L133         38 SEA FILE=USPATFULL ABB=ON  PLU=ON  RIFALAZIL OR ABI 1648 OR
                ABI1648 OR KRM1648 OR KRM 1648
L146            QUE  ABB=ON  PLU=ON  ?HEART? OR ?CARDIO? OR ?CARDIA? OR ?
                ANGINA? OR STROKE? OR ?CEREBR? OR ?BRAIN? OR ?CLAUDIC? OR
                 GANGREN? OR ?ISCHEM? OR ?ISCHAEM?
L147         28 SEA FILE=USPATFULL ABB=ON  PLU=ON  (L132 OR L133) AND L146


=> s (L135 or L151 or L147) not L159

L165    .    20 (L135 OR L151 OR L147) NOT L159
```

printed with author search

```
=> => dup rem L161 L162 L163 L164 L165
FILE 'HCAPLUS' ENTERED AT 12:02:20 ON 06 MAR 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'MEDLINE' ENTERED AT 12:02:20 ON 06 MAR 2006

FILE 'EMBASE' ENTERED AT 12:02:20 ON 06 MAR 2006
Copyright (c) 2006 Elsevier B.V. All rights reserved.

FILE 'BIOSIS' ENTERED AT 12:02:20 ON 06 MAR 2006
Copyright (c) 2006 The Thomson Corporation

FILE 'USPATFULL' ENTERED AT 12:02:20 ON 06 MAR 2006
CA INDEXING COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)
```

PROCESSING COMPLETED FOR L161
PROCESSING COMPLETED FOR L162
PROCESSING COMPLETED FOR L163
PROCESSING COMPLETED FOR L164
PROCESSING COMPLETED FOR L165
L166 40 DUP REM L161 L162 L163 L164 L165 (8 DUPLICATES REMOVED)
ANSWERS '1-2' FROM FILE HCAPLUS
ANSWERS '3-5' FROM FILE MEDLINE
ANSWERS '6-17' FROM FILE EMBASE
ANSWERS '18-20' FROM FILE BIOSIS
ANSWERS '21-40' FROM FILE USPATFULL

=> d ibib abs hitind hitstr L166 1-2; d iall L166 3-20; d ibib abs kwic hitstr L166 21-40

L166 ANSWER 1 OF 40 HCAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2003:149648 HCAPLUS
DOCUMENT NUMBER: 139:78195
TITLE: Development potential of **Rifalazil**
AUTHOR(S): Rothstein, David M.; Hartman, Arthur D.; Cynamon, Michael H.; Eisenstein, Barry I.
CORPORATE SOURCE: ActivBiotics, Inc., Cambridge, MA, 02139, USA
SOURCE: Expert Opinion on Investigational Drugs (2003), 12(2), 255-271
CODEN: EOIDER; ISSN: 1354-3784
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. **Rifalazil** represents a new generation of ansamycins that contain an unique 4-ring structure. Originally **Rifalazil** was developed as a therapeutic agent to replace rifampin as part of a multiple drug regimen in the treatment of tuberculosis. As a result of its superior antimicrobial activity and high intracellular levels, **Rifalazil** has the potential to treat indications caused by the intracellular pathogen, Chlamydia trachomatis, which causes nongonococcal urethritis and cervicitis, often leading to pelvic **inflammatory** disease. **Rifalazil** also has the potential to treat the related microorganism, Chlamydia pneumoniae, which may be involved in chronic **inflammatory** processes thought to be partly responsible for **atherosclerosis.** Due to its favorable antimicrobial spectrum and other pos. attributes, **Rifalazil** may also prove valuable in the treatment of gastric ulcer disease, caused by Helicobacter pylori, and antibiotic-associated colitis, the result of toxin production following the growth of Clostridium difficile in the colon. The potential value of **Rifalazil** in the treatment of these indications will be assessed in human clin. trials.
CC 1-0 (Pharmacology)
Section cross-reference(s): 14
ST review **Rifalazil** antimicrobial human
IT **Inflammation**
Intestine, disease
(colitis, antibiotic-associated; development potential of **Rifalazil** in human clin. trials)
IT Infection
(cutaneous; development potential of **Rifalazil** in human clin. trials)
IT Antimicrobial agents
Atherosclerosis
Human
Tuberculosis

(development potential of **Rifalazil** in human clin. trials)

IT Ulcer
(gastric; development potential of **Rifalazil** in human clin. trials)

IT Skin, disease
(infection; development potential of **Rifalazil** in human clin. trials)

IT Stomach, disease
(ulcer; development potential of **Rifalazil** in human clin. trials)

IT **129791-92-0, Rifalazil**
RL: **DMA (Drug mechanism of action)**; **PAC (Pharmacological activity)**; **PKT (Pharmacokinetics)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(development potential of **Rifalazil** in human clin. trials)

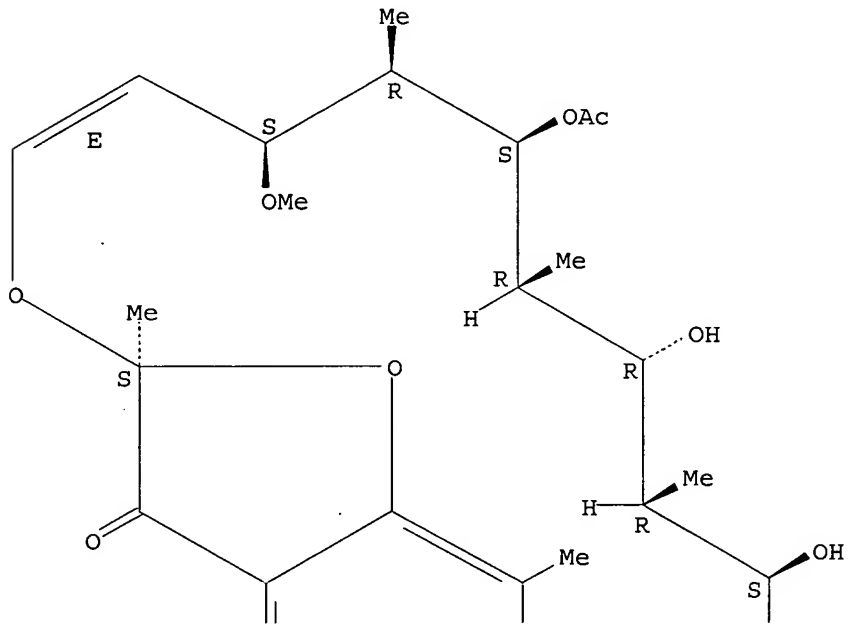
IT **129791-92-0, Rifalazil**
RL: **DMA (Drug mechanism of action)**; **PAC (Pharmacological activity)**; **PKT (Pharmacokinetics)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(development potential of **Rifalazil** in human clin. trials)

RN 129791-92-0 HCAPLUS

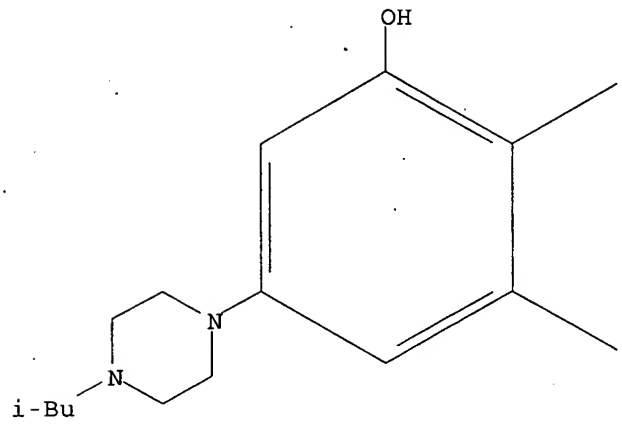
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

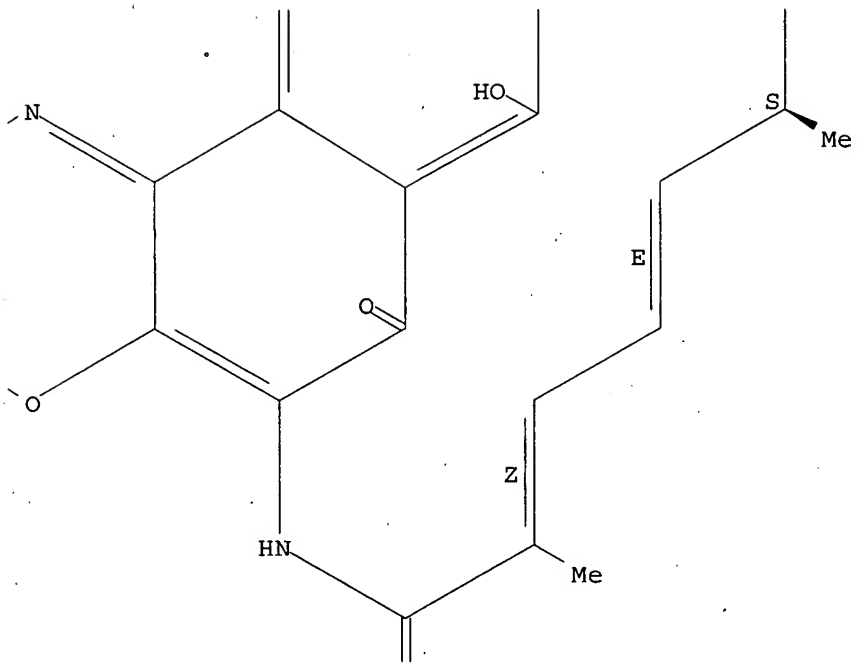
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

O

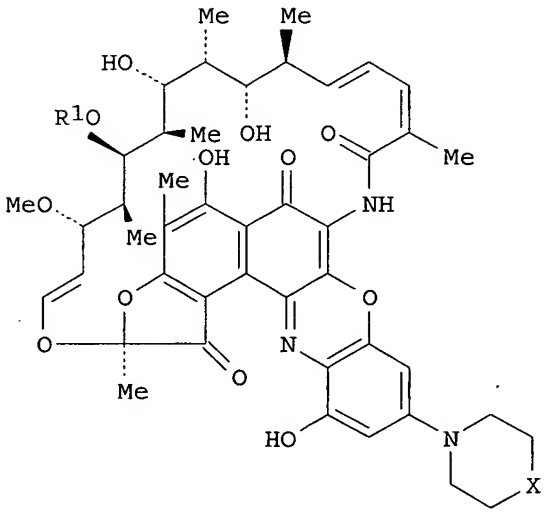
REFERENCE COUNT: 146 THERE ARE 146 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L166 ANSWER 2 OF 40 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1997:480833 HCAPLUS
DOCUMENT NUMBER: 127:117372
TITLE: Treatment of chlamydial infections with rifamycin derivatives
INVENTOR(S): Yamashita, Katsuji; Hosoe, Kazunori; Hidaka, Takayoshi; Todaro, George; Shawar, Ribhi M.
PATENT ASSIGNEE(S): Kaneka Corporation, Japan
SOURCE: Eur. Pat. Appl., 12 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
EP 778022	A1	19970611	EP 1996-119613		19961206
EP 778022	B1	20010411			
R: BE, CH, DE, ES, FR, GB, IT, LI					
JP 09216824	A2	19970819	JP 1996-2634		19960110
CA 2192255	AA	19970609	CA 1996-2192255		19961206
CA 2192255	C	20040713			
ES 2155566	T3	20010516	ES 1996-119613		19961206
US 5786349	A	19980728	US 1996-762501		19961209
PRIORITY APPLN. INFO.:			JP 1995-320882	A	19951208
			JP 1996-2634	A	19960110

OTHER SOURCE(S): MARPAT 127:117372
GI



I

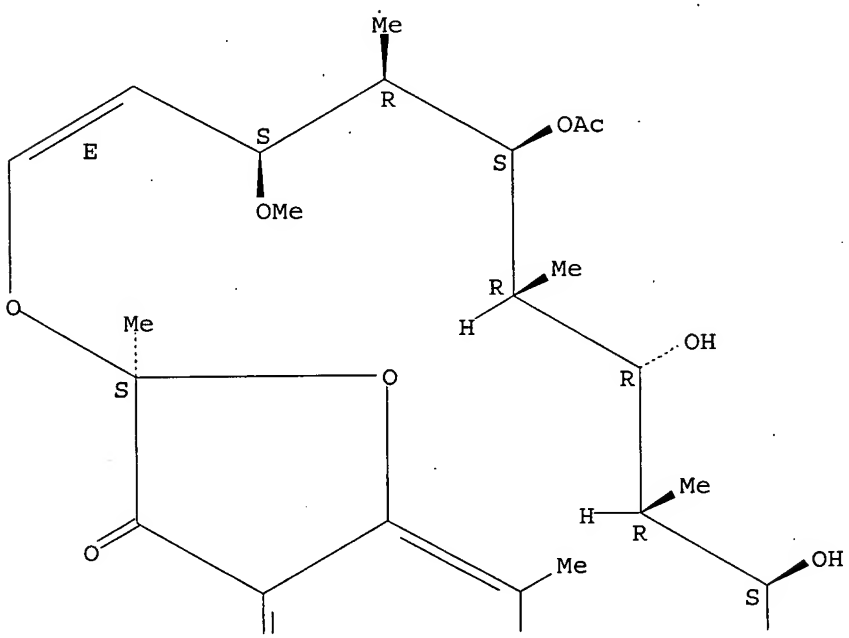
AB Trachoma, inclusion conjunctivitis, lymphogranuloma inguinale, nongonorrheal urethritis, psittacosis, atypical pneumonia, **coronary** disease, and other diseases caused by Chlamydia infection are treated with rifamycin derivs. I (R1 = H, Ac; X = O, S, NR; R = H, C1-7 alkyl, cycloalkyl, cycloalkylalkyl, 1,3-dioxolan-2-ylalkyl) or a physiol. acceptable salt thereof. Thus, I (R1 = Ac; X = NCH2CHMe2) (II) inhibited C. trachomatis in vitro with MIC = 0.000125 μg/mL and cured pneumonia from C. pneumoniae in mice at 1 mg/kg/day i.p. for 3 days.

Tablets containing 100 mg II were prepared from a granulated mixture of II 100, lactose 55, potato starch 41, and Mg stearate 4 g.

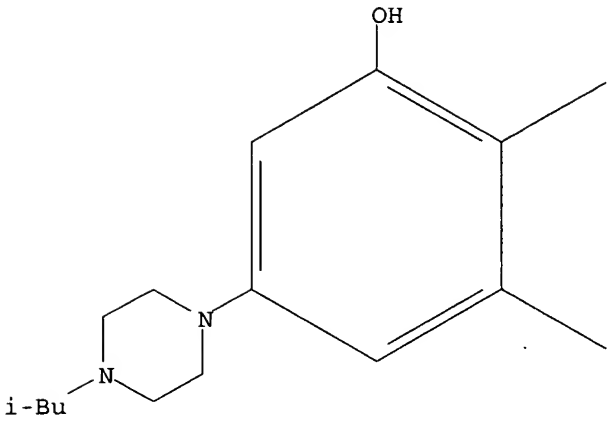
IC ICM A61K031-395
CC 1-5 (Pharmacology)
Section cross-reference(s): 10, 63
IT Artery, disease
(**coronary**; treatment of chlamydial infections with rifamycin derivs.)
IT 105396-59-6 **129791-92-0** 133633-12-2 143526-66-3
148236-03-7 188910-98-7
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(treatment of chlamydial infections with rifamycin derivs.)
IT **129791-92-0**
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(treatment of chlamydial infections with rifamycin derivs.)
RN 129791-92-0 HCAPLUS
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

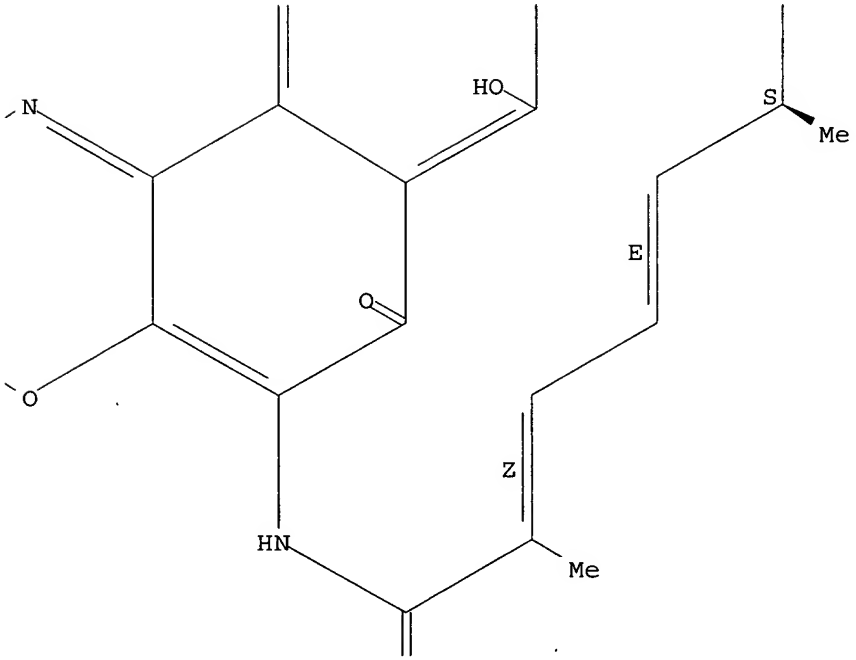
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

O

L166 ANSWER 3 OF 40 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER: 1999169748 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10049260
TITLE: Effects of the Chinese traditional medicine mao-bushi-saishin-to on therapeutic efficacy of a new benzoxazinorifamycin, **KRM-1648**, against Mycobacterium avium infection in mice.
AUTHOR: Shimizu T; Tomioka H; Sato K; Sano C; Akaki T; Dekio S; Yamada Y; Kamei T; Shibata H; Higashi N
CORPORATE SOURCE: Department of Microbiology and Immunology, Shimane Medical University, Japan.
SOURCE: Antimicrobial agents and chemotherapy, (1999 Mar) Vol. 43, No. 3, pp. 514-9.
Journal code: 0315061. ISSN: 0066-4804.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990712
Last Updated on STN: 19990712
Entered Medline: 19990622

ABSTRACT:
The Chinese traditional medicine mao-bushi-saishin-to (MBST), which has anti-inflammatory effects and has been used to treat the common cold and nasal allergy in Japan, was examined for its effects on the therapeutic activity of a new benzoxazinorifamycin, **KRM-1648** (KRM), against Mycobacterium avium complex (MAC) infection in mice. In addition, we examined the effects of MBST on the anti-MAC activity of murine peritoneal macrophages (M phi s). First, MBST significantly increased the anti-MAC therapeutic activity of KRM when given to mice in combination with KRM, although MBST alone did not exhibit such effects. Second, MBST treatment of M phi s significantly enhanced the KRM-mediated killing of MAC bacteria residing in M phi s, although MBST alone did not potentiate the M phi anti-MAC activity. MBST-treated M phi s showed decreased levels of reactive nitrogen intermediate (RNI) release, suggesting that RNIs are not decisive in the expression of the anti-MAC activity of such M phi populations. MBST partially blocked the interleukin-10 (IL-10) production of MAC-infected M phi s without affecting their transforming growth factor beta (TGF-beta)-producing activity. Reverse transcription-PCR analysis of the lung tissues of MAC-infected mice at weeks 4 and 8 after infection revealed a marked increase in the levels of tumor **necrosis** factor alpha, gamma interferon (IFN-gamma), IL-10, and TGF-beta mRNAs. KRM treatment of infected mice tended to decrease the levels of the test cytokine mRNAs, except that it increased TGF-beta mRNA expression at week 4. MBST treatment did not affect the levels of any cytokine mRNAs at week 8, while it down-regulated cytokine mRNA expression at week 4. At week 8, treatment of mice with a combination of KRM and MBST caused a marked decrease in the levels of the test cytokines mRNAs, especially IL-10 and IFN-gamma mRNAs, although such effects were obscure at week 4. These findings suggest that down-regulation of the expression of IL-10 and TGF-beta is related to the combined therapeutic effects of KRM and MBST against MAC infection.

CONTROLLED TERM: Check Tags: Female
Animals
*Anti-Bacterial Agents: TU, therapeutic use
Cytokines: BI, biosynthesis
Disease Models, Animal
Drug Synergism
*Drugs, Chinese Herbal: TU, therapeutic use
Free Radicals: ME, metabolism
Interleukin-10: BI, biosynthesis
Lung: DE, drug effects

Lung: ME, metabolism
Lung: MI, microbiology
Macrophages: DE, drug effects
Macrophages: ME, metabolism
Macrophages: MI, microbiology
Mice
Mice, Inbred BALB C
*Mycobacterium avium-intracellulare Infection: DT, drug therapy
Mycobacterium avium-intracellulare Infection: MI, microbiology
Nitrogen: ME, metabolism
RNA, Messenger: BI, biosynthesis
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, Non-P.H.S.
*Rifamycins: TU, therapeutic use
Transforming Growth Factor beta: BI, biosynthesis

CAS REGISTRY NO.: **129791-92-0 (KRM 1648)**; 130068-27-8 (Interleukin-10); 7727-37-9 (Nitrogen)

CHEMICAL NAME: 0 (Anti-Bacterial Agents); 0 (Cytokines); 0 (Drugs, Chinese Herbal); 0 (Free Radicals); 0 (RNA, Messenger); 0 (Rifamycins); 0 (Transforming Growth Factor beta); 0 (mao-bushi-saishin-to)

L166 ANSWER 4 OF 40 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 1999143907 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9925533
TITLE: Therapeutic effects of benzoxazinorifamycin **KRM-1648** administered alone or in combination with a half-sized secretory leukocyte protease inhibitor or the nonsteroidal anti-inflammatory drug diclofenac sodium against Mycobacterium avium complex infection in mice.
AUTHOR: Sano C; Shimizu T; Sato K; Kawauchi H; Kawahara S; Tomioka H
CORPORATE SOURCE: Department of Microbiology and Immunology, Shimane Medical University, Japan.
SOURCE: Antimicrobial agents and chemotherapy, (1999 Feb) Vol. 43, No. 2, pp. 360-4.
Journal code: 0315061. ISSN: 0066-4804.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990504
Last Updated on STN: 19990504
Entered Medline: 19990421

ABSTRACT:
The effects of half-sized secretory leukocyte protease inhibitor or diclofenac sodium administered alone or in combination with the benzoxazinorifamycin ***KRM*** **-1648** on the therapeutic efficacy of **KRM-** ***1648*** against Mycobacterium avium complex (MAC) in mice were studied. Neither of the two anti-inflammatory drugs affected the efficacy of **KRM -1648**, while they exerted significant modulating effects on tumor ***necrosis*** factor alpha production by MAC-infected macrophages.

CONTROLLED TERM: Animals
*Anti-Inflammatory Agents, Non-Steroidal: TU, therapeutic use
*Antibiotics, Antitubercular: TU, therapeutic use
Cytokines: ME, metabolism

*Diclofenac: TU, therapeutic use
Drug Therapy, Combination
Mice
Mice, Inbred BALB C
*Mycobacterium avium Complex: DE, drug effects
*Protease Inhibitors: TU, therapeutic use
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, Non-P.H.S.
*Rifamycins: TU, therapeutic use
*Tuberculosis: DT, drug therapy
CAS REGISTRY NO.: **129791-92-0 (KRM 1648)**; 15307-86-5 (Diclofenac)
CHEMICAL NAME: 0 (Anti-Inflammatory Agents, Non-Steroidal); 0 (Antibiotics, Antitubercular); 0 (Cytokines); 0 (Protease Inhibitors); 0 (Rifamycins)

L166 ANSWER 5 OF 40 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 97173286 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9021192
TITLE: Effects of benzoxazinorifamycin **KRM-1648** on cytokine production at sites of Mycobacterium avium complex infection induced in mice.
AUTHOR: Tomioka H; Sato K; Shimizu T; Sano C; Akaki T; Saito H; Fujii K; Hidaka T
CORPORATE SOURCE: Department of Microbiology and Immunology, Shimane Medical University, Japan.
SOURCE: Antimicrobial agents and chemotherapy, (1997 Feb) Vol. 41, No. 2, pp. 357-62.
Journal code: 0315061. ISSN: 0066-4804.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970514
Last Updated on STN: 19970514
Entered Medline: 19970505

ABSTRACT:
Although various antimicrobial agents exhibit appreciable microbicidal activity in the early phase (weeks 2 t0 4) of Mycobacterium avium complex (MAC) infection induced in mice, progressive bacterial regrowth subsequently occurs. To clarify the reason for this pattern of changes, we studied changes in the levels of various cytokines in tissue at sites of infection (spleens and lungs) of MAC-infected mice which were or were not given a benzoxazinorifamycin, ***KRM*** **-1648** (KRM). Levels of the proinflammatory cytokines tumor **necrosis** factor alpha (TNF-alpha) and gamma interferon (IFN-gamma) in tissues temporarily increased at around weeks 2 to 4 after infection, rapidly decreased thereafter, and returned to normal by week 8. Similar but somewhat delayed changes were noted for levels of interleukin 10 (IL-10) and transforming growth factor beta (TGF-beta), immunosuppressive cytokines with macrophage (M phi)-deactivating activity, in tissue, except that TGF-beta levels in the spleen remained high during weeks 4 to 8. KRM treatment blocked the increase in the levels of all of those cytokines in tissue in the early phase of infection, most strongly at week 4. IL-6 levels were beneath the limit of detection throughout the observation period. Bacterial loads in the visceral organs decreased during the first 2 weeks, and KRM treatment markedly promoted this decrease. However, regrowth of MAC organisms began at weeks 2 to 4 and continued thereafter, even in KRM-treated mice. Splenocytes and splenic M phi s of MAC-infected mice (week 2) produced and/or released into the culture fluid significant amounts of TNF-alpha (in a cell-bound form), IFN-gamma, and IL-10, but not TGF-beta, during 3 days of cultivation. A

substantial amount of TGF-beta was produced during 2 weeks of cultivation of peritoneal M phi s. KRM itself did not significantly affect the IL-10- and TGF-beta-producing ability of cultured M phi s. These findings suggest that IL-10 and TGF-beta play important roles in the regrowth of MAC organisms seen during the course of KRM treatment.

CONTROLLED TERM: Check Tags: Female
Animals
*Antibiotics, Antitubercular: PD, pharmacology
*Cytokines: BI, biosynthesis
Disease Models, Animal
Interferon Type II: BI, biosynthesis
Interleukin-10: BI, biosynthesis
Lung: DE, drug effects
Lung: ME, metabolism
Lung: MI, microbiology
Macrophages: DE, drug effects
Macrophages: ME, metabolism
Macrophages: MI, microbiology
Mice
Mice, Inbred BALB C
*Mycobacterium avium Complex: DE, drug effects
Mycobacterium avium Complex: ME, metabolism
*Mycobacterium avium-intracellulare Infection: DT, drug therapy
Mycobacterium avium-intracellulare Infection: ME, metabolism
Mycobacterium avium-intracellulare Infection: MI, microbiology
Research Support, Non-U.S. Gov't
*Rifamycins: PD, pharmacology
Spleen: DE, drug effects
Spleen: ME, metabolism
Spleen: MI, microbiology
Transforming Growth Factor beta: BI, biosynthesis
Tumor Necrosis Factor-alpha: BI, biosynthesis

CAS REGISTRY NO.: **129791-92-0 (KRM 1648)**; 130068-27-8 (Interleukin-10); 82115-62-6 (Interferon Type II)

CHEMICAL NAME: 0 (Antibiotics, Antitubercular); 0 (Cytokines); 0 (Rifamycins); 0 (Transforming Growth Factor beta); 0 (Tumor **Necrosis** Factor-alpha)

L166 ANSWER 6 OF 40 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 4

ACCESSION NUMBER: 1999051787 EMBASE

TITLE: Effects of Yokuinin on the therapeutic efficacy of a new benzoxazinorifamycin **KRM-1648** against Mycobacterium avium infection.

AUTHOR: Shimizu T.; Tomioka H.; Sato K.; Sano C.; Yamada Y.; Shibata H.; Higashi N.

CORPORATE SOURCE: H. Tomioka, Dept. Microbiology and Immunology, Shimane Medical University, Izumo, Shimane 693, Japan. tomioka@shimane-med.ac.jp

SOURCE: International Journal of Antimicrobial Agents, (1999) Vol. 11, No. 1, pp. 69-74. .
Refs: 26
ISSN: 0924-8579 CODEN: IAAGEA

PUBLISHER IDENT.: S 0924-8579(98)00078-8

COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis

030 Pharmacology
037 Drug Literature Index
004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19990304
Last Updated on STN: 19990304

ABSTRACT: The Chinese traditional medicine, Yokuinin, which has anti-inflammatory effects and anti-human papilloma virus activity, was examined for its effects on the therapeutic efficacy of a benzoxazinorifamycin ***KRM*** -1648 (KRM) against Mycobacterium avium infection in mice. Reverse transcription-PCR analysis revealed that Yokuinin increased the mRNA expression of all test cytokines in lung tissues of infected ice at week 8, in the order transforming growth factor-β (TGF-β)>IFN-γ>TNF-α>IL-10. Mice given Yokuinin in combination with KRM had higher levels of TFG-β mRNA expression than did mice given KRM alone, indicating that TGF-β plays an important role in the expression of the anti-inflammatory effect of Yokuinin in vivo. Yokuinin reduced IL-10 production by M. avium-infected macrophages ph. (MΦs) but did not affect MΦ TFG-β production. Although Yokuinin significantly modified cytokine expression in M. avium-infected mice, this drug did not influence the therapeutic efficacy of KRM against M. avium infection, suggesting that administration of Yokuinin in combination with KRM to the patients with M. avium infection does not cause severe disadvantages.

CONTROLLED TERM: Medical Descriptors:
*mycobacterium avium
mycobacteriosis: ET, etiology
mycobacteriosis: DT, drug therapy
reverse transcription polymerase chain reaction
chinese medicine
lung parenchyma
histochemistry
nonhuman
female
mouse
animal model
controlled study
animal tissue
oral drug administration
article
priority journal
Drug Descriptors:
*3' hydroxy 5' (4 isobutyl 1 piperazinyl)benzoxazinorifamycin: PD, pharmacology
*3' hydroxy 5' (4 isobutyl 1 piperazinyl)benzoxazinorifamycin: DT, drug therapy
*3' hydroxy 5' (4 isobutyl 1 piperazinyl)benzoxazinorifamycin: DO, drug dose
*3' hydroxy 5' (4 isobutyl 1 piperazinyl)benzoxazinorifamycin: CM, drug comparison
*3' hydroxy 5' (4 isobutyl 1 piperazinyl)benzoxazinorifamycin: CB, drug combination
*rifamycin derivative: PD, pharmacology
*rifamycin derivative: DT, drug therapy
*rifamycin derivative: DO, drug dose
*rifamycin derivative: CM, drug comparison
*rifamycin derivative: CB, drug combination
*chinese herb: PD, pharmacology
*chinese herb: DT, drug therapy

*chinese herb: CM, drug comparison
*chinese herb: CB, drug combination
messenger RNA: EC, endogenous compound
transforming growth factor beta: EC, endogenous compound
gamma interferon: EC, endogenous compound
tumor necrosis factor alpha: EC, endogenous compound
interleukin 10: EC, endogenous compound
yokuinin: PD, pharmacology
yokuinin: DT, drug therapy
yokuinin: CM, drug comparison
yokuinin: CB, drug combination

CAS REGISTRY NO.: (3' hydroxy 5' (4 isobutyl 1 piperazinyl)benzoxazinorifamycin) **129791-92-0**; (gamma interferon) 82115-62-6
CHEMICAL NAME: **(1) Krm 1648**
COMPANY NAME: (1) Kaneka (Japan); Kotaro Kampo Seiyaku (Japan)

L166 ANSWER 7 OF 40 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005075847 EMBASE
TITLE: Block copolymer micelles as a solution for drug delivery problems.
AUTHOR: Torchilin V.P.
CORPORATE SOURCE: V.P. Torchilin, Dept. of Pharmaceutical Sciences, Northeastern University, Boston, MA 02115, United States. v.torchilin@neu.edu
SOURCE: Expert Opinion on Therapeutic Patents, (2005) Vol. 15, No. 1, pp. 63-75. .
Refs: 121
ISSN: 1354-3776 CODEN: EOTPEG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
039 Pharmacy
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050303
Last Updated on STN: 20050303

ABSTRACT: Micelles, nanosized colloidal particles with a hydrophobic core and hydrophilic shell, can be successfully used for the solubilisation of various poorly soluble pharmaceuticals, and demonstrate a series of attractive properties as drug carriers. Polymeric micelles, such as micelles formed by amphiphilic block copolymers, are of a special interest as they possess high stability both in vitro and in vivo, and good biocompatibility. Drug-loaded micelles can spontaneously accumulate in body areas with compromised vasculature (tumours, **infarcts**) via the enhanced permeability and retention (EPR) effect. Micelles made of stimuli-responsive (pH- or temperature-sensitive) amphiphilic block copolymers can release their contents in pathological areas demonstrating hyperthermia or acidosis. Various specific targeting ligand molecules, such as antibodies, can be attached to the micelle surface and bring drug-loaded micelles to, and into, target cells (cancer cells being a primary target). Micelles carrying various reporter (contrast) groups may become the imaging agents of choice in different imaging modalities. This review will consider some recent trends in using micelles as pharmaceutical carriers. .COPYRGT. 2005 Ashley Publications Ltd.

CONTROLLED TERM: Medical Descriptors:
*drug delivery system

*micelle
nanoparticle
particle size
colloid
hydrophobicity
hydrophilicity
solubilization
in vitro study
in vivo study
biocompatibility
drug accumulation
vascular disease
drug penetration
stimulus response
pH
temperature sensitivity
drug release
hyperthermia
acidosis
gene targeting
cancer cell
diagnostic imaging
image enhancement
micellization
drug solubility
drug bioavailability
nonhuman
review
Drug Descriptors:
*copolymer
drug carrier
macrogol
phosphatidylethanolamine
rifalazil: PR, pharmaceutics
rifalazil: IV, intravenous drug administration
lipid
polymer
corticosteroid: PR, pharmaceutics
antiinflammatory agent: PR, pharmaceutics
piperazine derivative: PR, pharmaceutics
piperazine derivative: PO, oral drug administration
paclitaxel: PR, pharmaceutics
paclitaxel: PK, pharmacokinetics
paclitaxel: PO, oral drug administration
fentanyl: PR, pharmaceutics
carbamic acid ester: PR, pharmaceutics
carbamic acid ester: PD, pharmacology
camptothecin: PR, pharmaceutics
cisplatin: TO, drug toxicity
cisplatin: PR, pharmaceutics
cisplatin: IV, intravenous drug administration
nystatin: PR, pharmaceutics
propylene oxide
lysine
aspartic acid
anthracycline: PR, pharmaceutics
tsukubaenolide: PR, pharmaceutics
tsukubaenolide: PD, pharmacology
poly(ortho ester)
poly(methyl methacrylate)

tamoxifen: PR, pharmaceutics
porphyrin derivative: PR, pharmaceutics
povidone
haloperidol: PR, pharmaceutics
clonazepam: PR, pharmaceutics
amphotericin B: PR, pharmaceutics
unindexed drug

CAS REGISTRY NO.: (macrogol) 25322-68-3; (phosphatidylethanolamine) 1405-71-6; (**rifalazil**) **129791-92-0**; (lipid) 66455-18-3; (paclitaxel) 33069-62-4; (fentanyl) 437-38-7; (camptothecin) 7689-03-4; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (nystatin) 1400-61-9, 34786-70-4, 62997-67-5; (propylene oxide) 75-56-9; (lysine) 56-87-1, 6899-06-5, 70-54-2; (aspartic acid) 56-84-8, 6899-03-2; (tsukubaenolide) 104987-11-3; (poly(methyl methacrylate)) 39320-98-4, 9008-29-1; (tamoxifen) 10540-29-1; (povidone) 9003-39-8; (haloperidol) 52-86-8; (clonazepam) 1622-61-3; (amphotericin B) 1397-89-3, 30652-87-0

CHEMICAL NAME: Fk 506

L166 ANSWER 8 OF 40 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2005123422 EMBASE
TITLE: Gateways to Clinical Trials: January/February 2005.
AUTHOR: Bayes M.; Rabasseda X.; Prous J.R.
SOURCE: Methods and Findings in Experimental and Clinical Pharmacology, (2005) Vol. 27, No. 1, pp. 49-77. .
Refs: 162
ISSN: 0379-0355 CODEN: MFEPDX
COUNTRY: Spain
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20050331
Last Updated on STN: 20050331

ABSTRACT: Gateways to Clinical Trials is a guide to the most recent clinical trials reported in current literature and congresses. The data in the following tables have been retrieved from the Clinical Trials Knowledge Area of Prous Science Integrity®, the drug discovery and development portal, http://integrity. prous.com. This issue focuses on the following selection of drugs: [188Re]-HDD; A-179578, adalimumab, AK-602, albumin interferon alfa, alfimeprase, amelubant, anakinra, anti-CD2 MAb, APD-356, aripiprazole, atvogen; Bimatoprost, bimosiamose, BLP-25, brivaracetam; Caspofungin acetate, cilansetron, CMV vaccine (bivalent), conivaptan hydro chloride, Cypher; Darbepoetin alfa, darifenacin hydrobromide, D-D4FC, decitabine, dnaJP1, doranidazole, dronedarone hydrochloride; Efalizumab, efaproxiral sodium, emtricitabine, Endeavor, entecavir, erlotinib hydrochloride, escitalopram oxalate, etoricoxib, etravirine, ezetimibe; Fampridine, fenretinide, ferumoxtran-10, forodesine hydrochloride; Gantacurium chloride, gemifloxacin mesilate, Glyminox, GW-501516; HBV-ISS, hepavir B, human insulin, HuMax-CD20, hyaluronic acid, HyCAMP; Icatibant, IDEA-070, IGN-311, imatinib mesylate, insulin detemir, insulin glargine, insulin glulisine; Lapatinib, lasofoxifene tartrate, LB-80380, liarozolefumarate, liposome encapsulated doxorubicin, lumiracoxib, LY-570310; MC-1, melatonin, merimepodib, metanicotine, midostaurin; Natalizumab, nicotine conjugate vaccine, NYVAC-HIV C; Patupilone, peginterferon alfa-2a, peginterferon alfa-2b, peginterferon alfa-2b/ribavirin, pelitinib, Peru-15, pexelizumab, PHP, pimecrolimus, prednisolone sodium metasulfobenzoate; Recombinant α(1)-antitrypsin (AAT), retigabine, rHA

influenza vaccine, **rifalazil**, rofecoxib, rosiglitazone maleate/Metformin hydrochloride, rostaporfin, rosuvastatin calcium, rubitecan; Selenite sodium; semilente insulin, SMP-797, sorafenib; Talampanel, tenofovir disoproxil fumarate, TER-199, tiotropium bromide, torcetrapib, treprostinil sodium, TTA; ValboroPro, valdecoxib, val-mCyd, valtorcitabine dihydrochloride: XP-828L.

CONTROLLED TERM: Medical Descriptors:
*drug research
drug safety
drug tolerability
drug efficacy
anemia: CO, complication
anemia: DT, drug therapy
kidney failure: TH, therapy
hemodialysis
blood disease: DT, drug therapy
lymphatic system disease: DT, drug therapy
eye disease: DT, drug therapy
gastrointestinal disease: DT, drug therapy
vagina atrophy: DT, drug therapy
osteoporosis: DT, drug therapy
vulvovaginitis: DT, drug therapy
Behcet disease: DT, drug therapy
genital ulcer: DT, drug therapy
chronic fatigue syndrome: DT, drug therapy
postoperative pain: DT, drug therapy
immunopathology: DT, drug therapy
virus infection: DT, drug therapy
respiratory tract infection: DT, drug therapy
metabolic disorder: DT, drug therapy
nutritional disorder: DT, drug therapy
insulin dependent diabetes mellitus: DT, drug therapy
non insulin dependent diabetes mellitus: DT, drug therapy
hypercholesterolemia: DT, drug therapy
hyperlipidemia: DT, drug therapy
musculoskeletal disease: DT, drug therapy
connective tissue disease: DT, drug therapy
bone disease: DT, drug therapy
rheumatoid arthritis: DT, drug therapy
osteoarthritis: DT, drug therapy
ankylosing spondylitis: DT, drug therapy
ischialgia: DT, drug therapy
acquired immune deficiency syndrome
Kaposi sarcoma: CO, complication
Kaposi sarcoma: DT, drug therapy
lung tumor: DT, drug therapy
bladder cancer: DT, drug therapy
brain cancer: DT, drug therapy
breast cancer: DT, drug therapy
colon cancer: DT, drug therapy
colorectal cancer: DT, drug therapy
rectum cancer: DT, drug therapy
liver cancer: DT, drug therapy
pancreas cancer: DT, drug therapy
prostate cancer: DT, drug therapy
leukemia: DT, drug therapy
uterus cancer: DT, drug therapy
lymphoma: DT, drug therapy
myelodysplasia: DT, drug therapy

neurologic disease: DT, drug therapy
epilepsy: DT, drug therapy
nystagmus: DT, drug therapy
mental disease: DT, drug therapy
depression: DT, drug therapy
schizophrenia: DT, drug therapy
kidney disease: DT, drug therapy
urinary tract disease: DT, drug therapy
respiratory tract disease: DT, drug therapy
mediastinum disease: DT, drug therapy
skin disease: DT, drug therapy
ichthyosis: DT, drug therapy
psoriasis: DT, drug therapy
smoking cessation
coronary artery disease: DT, drug therapy
vascular disease: DT, drug therapy
thrombosis: DT, drug therapy
human
clinical trial
review
Drug Descriptors:
adalimumab: CT, clinical trial
adalimumab: DT, drug therapy
4 [4 [1 butyl 3 (cyclohexylhydroxymethyl) 2,5 dioxo 1,4,9 triazaspiro[5.5]undec 9 ylmethyl]phenoxy]benzoic acid: CT, clinical trial
4 [4 [1 butyl 3 (cyclohexylhydroxymethyl) 2,5 dioxo 1,4,9 triazaspiro[5.5]undec 9 ylmethyl]phenoxy]benzoic acid: DT, drug therapy
albumin alpha interferon: CT, clinical trial
albumin alpha interferon: DT, drug therapy
alfimeprase: CT, clinical trial
alfimeprase: DT, drug therapy
amelubant: CT, clinical trial
amelubant: DT, drug therapy
recombinant interleukin 1 receptor blocking agent: CT, clinical trial
recombinant interleukin 1 receptor blocking agent: DT, drug therapy
apd 356: CT, clinical trial
apd 356: DT, drug therapy
aripiprazole: CT, clinical trial
aripiprazole: DT, drug therapy
atvogen: CT, clinical trial
atvogen: DT, drug therapy
bimatoprost: CT, clinical trial
bimatoprost: DT, drug therapy
bimosiamose: CT, clinical trial
bimosiamose: DT, drug therapy
blp 25: CT, clinical trial
blp 25: DT, drug therapy
brivaracetam: CT, clinical trial
brivaracetam: DT, drug therapy
caspofungin: CT, clinical trial
caspofungin: DT, drug therapy
cilansetron: CT, clinical trial
cilansetron: DT, drug therapy
Cytomegalovirus vaccine: CT, clinical trial
Cytomegalovirus vaccine: DT, drug therapy
conivaptan: CT, clinical trial

conivaptan: DT, drug therapy
novel erythropoiesis stimulating protein: CT, clinical trial
novel erythropoiesis stimulating protein: DT, drug therapy
darifenacin: CT, clinical trial
darifenacin: DT, drug therapy
5 aza 2' deoxycytidine: CT, clinical trial
5 aza 2' deoxycytidine: DT, drug therapy
doranidazole: CT, clinical trial
doranidazole: DT, drug therapy
dronedarone: CT, clinical trial
dronedarone: DT, drug therapy

CONTROLLED TERM: Drug Descriptors:
efalizumab: CT, clinical trial
efalizumab: DT, drug therapy
efaproxiral: CT, clinical trial
efaproxiral: DT, drug therapy
emtricitabine: CT, clinical trial
emtricitabine: DT, drug therapy
entecavir: CT, clinical trial
entecavir: DT, drug therapy
erlotinib: CT, clinical trial
erlotinib: DT, drug therapy
escitalopram: CT, clinical trial
escitalopram: DT, drug therapy
etoricoxib: CT, clinical trial
etoricoxib: DT, drug therapy
unindexed drug
unclassified drug
d d4fc
gw 501516
idea 070
ign 311
2 amino 9 (1 phosphonomethoxycyclopropylmethyl)purine bis(pivaloyloxymethyl) ester
Peru 15
smp 797
gamma glutamyl s benzylcysteinylphenylglycine diethyl ester
xp 8281

CAS REGISTRY NO.: (adalimumab) 331731-18-1; (alfimeprase) 259074-76-5; (aripiprazole) 129722-12-9; (bimatoprost) 155206-00-1; (bimosiamose) 187269-40-5, 187269-60-9; (caspofungin) 189768-38-5; (cilansetron) 120635-72-5, 120635-74-7, 209859-87-0; (conivaptan) 168626-94-6, 210101-16-9; (darifenacin) 133099-04-4, 133099-07-7; (5 aza 2' deoxycytidine) 2353-33-5; (dronedarone) 141626-36-0; (efalizumab) 214745-43-4; (efaproxiral) 131179-95-8, 170787-99-2; (emtricitabine) 137530-41-7, 143491-54-7, 143491-57-0; (entecavir) 142217-69-4, 209216-23-9; (erlotinib) 183319-69-9, 183321-74-6; (escitalopram) 128196-01-0, 219861-08-2; (etoricoxib) 202409-33-4, 202409-40-3; (gw 501516) 317318-70-0

CHEMICAL NAME: Apd 356; D d4fc; Blp 25; Gw 501516; Idea 070; Ign 311; Lb 80380; Peru 15; Smp 797; Ter 199; Xp 8281

L166 ANSWER 9 OF 40 EMBASE

ACCESSION NUMBER: 2004281749 EMBASE

TITLE: Comparison of inhibitory effect of **rifalazil** and rifampicin against Mycobacterium ulcerans infection induced

in mice.

AUTHOR: Nakanaga K.; Saito H.; Ishii N.; Goto M.
CORPORATE SOURCE: K. Nakanaga, Department of Bioregulation, Leprosy Research Center, Natl. Inst. of Infectious Diseases, 4-2-1, Aoba-cho, Higashimurayama-shi, Tokyo 189-0002, Japan. nakanaga@nih.go.jp

SOURCE: Kekkaku, (2004) Vol. 79, No. 5, pp. 333-339. .
Refs: 38
ISSN: 0022-9776 CODEN: KEKKAG
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
013 Dermatology and Venereology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: Japanese
SUMMARY LANGUAGE: English; Japanese
ENTRY DATE: Entered STN: 20040722
Last Updated on STN: 20040722

ABSTRACT: [Purpose] Buruli ulcer is a human skin disease caused by Mycobacterium ulcerans infection, which is characterized by massive skin ulceration and persistent necrotic change. In recent years Buruli ulcer has rapidly emerged as an increasingly important cause of human morbidity around the world. The disease is endemic at least 32 countries in Africa, Western Pacific, Asia and South America, and it is considered the third most common mycobacterial infection of humans after tuberculosis and leprosy. An effective chemotherapeutic regimen against Buruli ulcer disease has not been established to date. In this study, the inhibitory effect of **rifalazil** (RLZ) against M. ulcerans was assessed in experimentally infected mice and compared to that of rifampicin (RFP). [Materials and Methods] Five-week-old BALB/c female mice were challenged with 25 μl (CFU = 4 x 10(4)) of M. ulcerans cultured in Middlebrook 7H9 broth in bilateral hind footpads. Mice were administered per os with a suspension of RLZ or RFP at 2.5, 5, or 10 mg/kg once daily 5 times per week starting from one day up to 6 weeks after infection. During the treatment, mice were observed weekly for footpad skin lesions and examined for footpad swelling. In addition, CFU enumeration was done on both hind footpads and spleen at 2, 4, and 6 weeks after initiating treatment. [Results] In the infected control mice group, slightly erythematous lesions and moderate swelling of footpads were observed 4 weeks after the infection. Ulcerative lesion was observed 6 weeks after the infection. Mean log(10) CFU/footpad (FP) was 5.22 on day 1 after the infection and increased to 5.56, 6.29, and 7.33 at 2, 4, and 6 weeks after treatment was initiated in the treated groups. On the other hand, no visible erythema, swelling or ulcerative lesion in footpads were observed in RLZ-administered groups. Furthermore, log(10)CFU/FP decreased to 4.14 after only 2 weeks of initiating treatment in 2.5 mg/kg administered group, i.e. the lowest dose employed group. Log(10) CFU/FP decreased to < 2.1 in 6 weeks in the 10 mg/kg administered group, which was close to the detection limit (< 1.7) of the CFU assay. By contrast, inhibitory effect on disease progression and reduction of CFU were observed only in the group of mice given 10 mg/kg among RFP-administered groups; the reduction of CFU was not observed in the early period but 6 weeks after initiating treatment. [Conclusion] These results clearly demonstrate that the in vivo anti-M. ulcerans activity of RLZ is much higher than RFP. RLZ activity against M. ulcerans can be expected to control the disease progression in the clinical applications.

CONTROLLED TERM: Medical Descriptors:
*inhibition kinetics
*Mycobacterium ulcerans
*Buruli ulcer: DT, drug therapy

*Buruli ulcer: EP, epidemiology
*Buruli ulcer: ET, etiology
treatment outcome
skin ulcer: ET, etiology
skin necrosis: ET, etiology
clinical feature
bacterium culture
foot pad
colony forming unit
erythema
in vivo study
drug efficacy
nonhuman
mouse
animal model
controlled study
article
Drug Descriptors:
***rifalazil: CM, drug comparison**
***rifalazil: DT, drug therapy**
***rifalazil: PD, pharmacology**
***rifalazil: PO, oral drug administration**
*rifampicin: CM, drug comparison
*rifampicin: DT, drug therapy
*rifampicin: PD, pharmacology
*rifampicin: PO, oral drug administration
streptomycin
amikacin
dapsone
CAS REGISTRY NO.: (**rifalazil**) **129791-92-0**; (rifampicin) 13292-46-1; (streptomycin) 57-92-1; (amikacin) 37517-28-5, 39831-55-5; (dapsone) 80-08-0

L166 ANSWER 10 OF 40 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2003318278 EMBASE
TITLE: Recent developments in the treatment of tuberculosis.
AUTHOR: Davies P.D.O.; Yew W.W.
CORPORATE SOURCE: Dr. P.D.O. Davies, Tuberculosis Research Unit, Cardiothoracic Centre, Liverpool L14 3PE, United Kingdom. Peter.Davies2@ccl-tr.nwest.nhs.uk
SOURCE: Expert Opinion on Investigational Drugs, (1 Aug 2003) Vol. 12, No. 8, pp. 1297-1312.
Refs: 151
ISSN: 1354-3784 CODEN: EOIDER
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
015 Chest Diseases, Thoracic Surgery and Tuberculosis
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20030821
Last Updated on STN: 20030821
ABSTRACT: The history of chemotherapy of tuberculosis commenced in 1944 with the discovery of streptomycin. Currently, short-course chemotherapy comprising rifampicin, isoniazid, pyrazinamide and ethambutol/streptomycin administered under directly observed settings for 6 months (initially all four drugs

followed by the former two drugs), constitutes the cornerstone treatment for pulmonary tuberculosis. Multi-drug resistant tuberculosis requires alternative chemotherapy, ideally in the form of individualised regimens, for management. To improve on the duration of chemotherapy for drug-susceptible tuberculosis and to achieve better treatment for multi-drug resistant tuberculosis as well as latent tuberculosis infection, there arises a genuine need for new drugs. The quest for new agents is, however, impeded by obstacles. Hopefully, tackling these through collaborative public-private partnerships on an international scale will lead to a fruitful outcome.

CONTROLLED TERM: Medical Descriptors:
*lung tuberculosis: DI, diagnosis
*lung tuberculosis: DM, disease management
*lung tuberculosis: DR, drug resistance
*lung tuberculosis: DT, drug therapy
*lung tuberculosis: ET, etiology
*lung tuberculosis: SU, surgery
short course therapy
directly observed therapy
multidrug resistance
individualization
drug sensitivity
public health service
international cooperation
treatment outcome
sputum smear
world health organization
bacterium culture
health care delivery
thorax radiography
Mycobacterium tuberculosis
minimum inhibitory concentration
drug penetration
drug tolerance
photosensitivity: SI, side effect
heart disease: SI, side effect
drug half life
lung resection
cost effectiveness analysis
human
nonhuman
review
Drug Descriptors:
***tuberculostatic agent: AE, adverse drug reaction**
***tuberculostatic agent: CB, drug combination**
***tuberculostatic agent: DV, drug development**
*tuberculostatic agent: DT, drug therapy
*tuberculostatic agent: PE, pharmacoeconomics
streptomycin: AE, adverse drug reaction
streptomycin: CB, drug combination
streptomycin: DT, drug therapy
streptomycin: PE, pharmacoeconomics
rifampicin: AE, adverse drug reaction
rifampicin: CB, drug combination
rifampicin: DT, drug therapy
rifampicin: PE, pharmacoeconomics
isoniazid: AE, adverse drug reaction
isoniazid: CB, drug combination
isoniazid: DT, drug therapy
isoniazid: PE, pharmacoeconomics

pyrazinamide: AE, adverse drug reaction
pyrazinamide: CB, drug combination
pyrazinamide: DT, drug therapy
pyrazinamide: PE, pharmacoeconomics
ethambutol: AE, adverse drug reaction
ethambutol: CB, drug combination
ethambutol: DT, drug therapy
ethambutol: PE, pharmacoeconomics
aminosalicylic acid: AE, adverse drug reaction
aminosalicylic acid: CB, drug combination
aminosalicylic acid: DT, drug therapy
aminosalicylic acid: PE, pharmacoeconomics
thioacetazone: AE, adverse drug reaction
thioacetazone: CB, drug combination
thioacetazone: DT, drug therapy
thioacetazone: PE, pharmacoeconomics
quinoline derived antiinfective agent: CB, drug combination
quinoline derived antiinfective agent: DT, drug therapy
quinoline derived antiinfective agent: PE, pharmacoeconomics
quinoline derived antiinfective agent: PK, pharmacokinetics
levofloxacin: AE, adverse drug reaction
levofloxacin: CB, drug combination
levofloxacin: CM, drug comparison
levofloxacin: DT, drug therapy
levofloxacin: PK, pharmacokinetics
ofloxacin: AE, adverse drug reaction
ofloxacin: CB, drug combination
ofloxacin: CM, drug comparison
ofloxacin: DT, drug therapy
ofloxacin: PK, pharmacokinetics
aminoglycoside antibiotic agent: AE, adverse drug reaction
aminoglycoside antibiotic agent: CB, drug combination
aminoglycoside antibiotic agent: DT, drug therapy
ethionamide: AE, adverse drug reaction
ethionamide: CB, drug combination
ethionamide: DT, drug therapy
protionamide: AE, adverse drug reaction
protionamide: CB, drug combination
protionamide: DT, drug therapy
cycloserine: AE, adverse drug reaction
cycloserine: CB, drug combination
cycloserine: DT, drug therapy
ciprofloxacin: CB, drug combination
ciprofloxacin: DT, drug therapy
ciprofloxacin: PK, pharmacokinetics
sparfloxacin: AE, adverse drug reaction
sparfloxacin: CM, drug comparison
sparfloxacin: DT, drug therapy
moxifloxacin: AE, adverse drug reaction
moxifloxacin: DT, drug therapy
sitafloxacin: AE, adverse drug reaction
sitafloxacin: DT, drug therapy
gatifloxacin: AE, adverse drug reaction
gatifloxacin: DT, drug therapy
1 cyclopropyl 8 difluoromethoxy 7 (2,3 dihydro 1 methyl 1h isoindol 5 yl) 1,4 dihydro 4 oxo 3 quinolinecarboxylic acid: AE, adverse drug reaction
1 cyclopropyl 8 difluoromethoxy 7 (2,3 dihydro 1 methyl 1h isoindol 5 yl) 1,4 dihydro 4 oxo 3 quinolinecarboxylic

acid: DV, drug development
1 cyclopropyl 8 difluoromethoxy 7 (2,3 dihydro 1 methyl 1h isoindol 5 yl) 1,4 dihydro 4 oxo 3 quinolinecarboxylic acid: DT, drug therapy
1 cyclopropyl 8 difluoromethoxy 7 (2,3 dihydro 1 methyl 1h isoindol 5 yl) 1,4 dihydro 4 oxo 3 quinolinecarboxylic acid: PK, pharmacokinetics
1 cyclopropyl 8 difluoromethoxy 7 (2,3 dihydro 1 methyl 1h isoindol 5 yl) 1,4 dihydro 4 oxo 3 quinolinecarboxylic acid: PO, oral drug administration
1 cyclopropyl 7 (3 ethyl 1 piperazinyl) 6 fluoro 1,4 dihydro 8 methoxy 4 oxo 3 quinolinecarboxylic acid: AE, adverse drug reaction
1 cyclopropyl 7 (3 ethyl 1 piperazinyl) 6 fluoro 1,4 dihydro 8 methoxy 4 oxo 3 quinolinecarboxylic acid: DV, drug development
1 cyclopropyl 7 (3 ethyl 1 piperazinyl) 6 fluoro 1,4 dihydro 8 methoxy 4 oxo 3 quinolinecarboxylic acid: DT, drug therapy
1 cyclopropyl 7 (3 ethyl 1 piperazinyl) 6 fluoro 1,4 dihydro 8 methoxy 4 oxo 3 quinolinecarboxylic acid: PK, pharmacokinetics
1 cyclopropyl 7 (3 ethyl 1 piperazinyl) 6 fluoro 1,4 dihydro 8 methoxy 4 oxo 3 quinolinecarboxylic acid: PO, oral drug administration
rifabutin: CB, drug combination
rifabutin: CM, drug comparison
rifabutin: DV, drug development
rifabutin: DT, drug therapy

CONTROLLED TERM: Drug Descriptors:
rifalazil: CB, drug combination
rifalazil: CM, drug comparison
rifalazil: DT, drug therapy
rifapentine: CB, drug combination
rifapentine: DV, drug development
rifapentine: DT, drug therapy
rifamycin derivative: CM, drug comparison
rifamycin derivative: CR, drug concentration
rifamycin derivative: DV, drug development
rifamycin derivative: DT, drug therapy
rifamycin derivative: PD, pharmacology
paromomycin: DV, drug development
paromomycin: DT, drug therapy
tobramycin: DV, drug development
tobramycin: DT, drug therapy
oxazolidinone derivative: DV, drug development
oxazolidinone derivative: DT, drug therapy
unindexed drug

CAS REGISTRY NO.: (streptomycin) 57-92-1; (rifampicin) 13292-46-1; (isoniazid) 54-85-3, 62229-51-0, 65979-32-0; (pyrazinamide) 98-96-4; (ethambutol) 10054-05-4, 1070-11-7, 3577-94-4, 74-55-5; (aminosalicylic acid) 133-10-8, 133-15-3, 28088-64-4, 51540-64-8, 65-49-6, 80702-32-5; (thioacetazone) 104-06-3; (levofloxacin) 100986-85-4, 138199-71-0; (ofloxacin) 82419-36-1; (ethionamide) 536-33-4; (protionamide) 14222-60-7; (cycloserine) 339-72-0, 68-39-3, 68-41-7; (ciprofloxacin) 85721-33-1; (sparfloxacin) 111542-93-9; (moxifloxacin) 151096-09-2; (sitafloxacin) 127254-12-0, 163253-35-8; (gatifloxacin) 112811-59-3, 180200-66-2; (1 cyclopropyl 8 difluoromethoxy

7 (2,3 dihydro 1 methyl 1h isoindol 5 yl) 1,4 dihydro 4 oxo 3 quinolinecarboxylic acid) 194804-75-6, 223652-82-2, 223652-90-2; (1 cyclopropyl 7 (3 ethyl 1 piperazinyl) 6 fluoro 1,4 dihydro 8 methoxy 4 oxo 3 quinolinecarboxylic acid) 183135-57-1; (rifabutin) 72559-06-9; (**rifalazil**) **129791-92-0**; (rifapentine) 61379-65-5; (paromomycin) 11035-13-5, 1263-89-4, 1390-73-4, 51795-47-2, 54597-56-7, 7542-37-2, 84420-34-8; (tobramycin) 32986-56-4

CHEMICAL NAME: Du 6859a; T 3811 me; Pd 161148

L166 ANSWER 11 OF 40 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2003305175 EMBASE

TITLE: Digestive Disease Week 2003 17-22 May 2003, Orlando, FL, USA.

AUTHOR: Gotham S.

CORPORATE SOURCE: S. Gotham, Thomson Current Drugs, Middlesex House, 34-42 Cleveland Street, London W1T 4JE, United Kingdom. sue.gotham@current-drugs.com

SOURCE: IDrugs, (1 Jul 2003) Vol. 6, No. 7, pp. 631-634. . ISSN: 1369-7056 CODEN: IDRUFN

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Conference Article

FILE SEGMENT: 048 Gastroenterology
016 Cancer
004 Microbiology
037 Drug Literature Index
038 Adverse Reactions Titles
036 Health Policy, Economics and Management
030 Pharmacology

LANGUAGE: English

ENTRY DATE: Entered STN: 20030814
Last Updated on STN: 20030814

CONTROLLED TERM: Medical Descriptors:
*gastrointestinal disease: DT, drug therapy
*gastrointestinal disease: SI, side effect
*gastrointestinal disease: PC, prevention
*gastrointestinal disease: DM, disease management
*gastrointestinal disease: DR, drug resistance
human
clinical trial
nonhuman
digestive system cancer: PC, prevention
digestive system cancer: DT, drug therapy
cancer prevention
digestive system infection: DT, drug therapy
digestive system infection: DM, disease management
digestive system infection: DR, drug resistance
gastroesophageal reflux: DT, drug therapy
analgesia
pain: DT, drug therapy
inflammatory disease: DT, drug therapy
cardiovascular disease: SI, side effect
cardiovascular disease: DT, drug therapy
cardiovascular disease: PC, prevention
drug potentiation
low drug dose
digestive system injury: SI, side effect
digestive system injury: DT, drug therapy

digestive system injury: PC, prevention
dyspepsia: SI, side effect
abdominal pain: SI, side effect
drug withdrawal
gastrointestinal symptom: SI, side effect
gastrointestinal symptom: DT, drug therapy
gastrointestinal symptom: PC, prevention
stomach mucosa injury: SI, side effect
stomach mucosa injury: DT, drug therapy
stomach mucosa injury: PC, prevention
gastrointestinal hemorrhage: SI, side effect
protein losing gastroenteropathy: SI, side effect
anemia: SI, side effect
dose response
drug effect
drug mechanism
stomach protection
stomach ulcer: SI, side effect
drug blood level
cancer chemotherapy
drug efficacy
single drug dose
area under the curve
drug half life
drug tolerability
drug cost
nausea and vomiting: SI, side effect
treatment failure
antibiotic resistance
conference paper
Drug Descriptors:
*gastrointestinal agent: DT, drug therapy
*gastrointestinal agent: PD, pharmacology
*gastrointestinal agent: AE, adverse drug reaction
*gastrointestinal agent: CT, clinical trial
*gastrointestinal agent: CB, drug combination
*gastrointestinal agent: IT, drug interaction
*gastrointestinal agent: IG, intragastric drug administration
*gastrointestinal agent: DO, drug dose
*gastrointestinal agent: CM, drug comparison
*gastrointestinal agent: PO, oral drug administration
*gastrointestinal agent: CR, drug concentration
*gastrointestinal agent: PK, pharmacokinetics
*gastrointestinal agent: PE, pharmacoeconomics
cyclooxygenase 2 inhibitor: DT, drug therapy
cyclooxygenase 2 inhibitor: PD, pharmacology
cyclooxygenase 2 inhibitor: AE, adverse drug reaction
cyclooxygenase 2 inhibitor: CB, drug combination
cyclooxygenase 2 inhibitor: IT, drug interaction
cyclooxygenase 2 inhibitor: CM, drug comparison
cyclooxygenase 2 inhibitor: CT, clinical trial
cyclooxygenase 2 inhibitor: PO, oral drug administration
acetylsalicylic acid: DT, drug therapy
acetylsalicylic acid: PD, pharmacology
acetylsalicylic acid: AE, adverse drug reaction
acetylsalicylic acid: CB, drug combination
acetylsalicylic acid: IT, drug interaction
acetylsalicylic acid: IG, intragastric drug administration
acetylsalicylic acid: DO, drug dose

acetylsalicylic acid: CM, drug comparison
acetylsalicylic acid: PO, oral drug administration
acetylsalicylic acid: CT, clinical trial
alpha tocopherol derivative: DT, drug therapy
alpha tocopherol derivative: PD, pharmacology
alpha tocopherol derivative: DO, drug dose
alpha tocopherol derivative: IP, intraperitoneal drug administration
2 (alpha dextro glucopyranosyl)methyl 2,5,7,8 tetramethylchroman 6 ol: DT, drug therapy
2 (alpha dextro glucopyranosyl)methyl 2,5,7,8 tetramethylchroman 6 ol: PD, pharmacology
2 (alpha dextro glucopyranosyl)methyl 2,5,7,8 tetramethylchroman 6 ol: DO, drug dose
2 (alpha dextro glucopyranosyl)methyl 2,5,7,8 tetramethylchroman 6 ol: IP, intraperitoneal drug administration
indometacin: DT, drug therapy
indometacin: PD, pharmacology
indometacin: AE, adverse drug reaction
nonsteroid antiinflammatory agent: DT, drug therapy
nonsteroid antiinflammatory agent: PD, pharmacology
nonsteroid antiinflammatory agent: AE, adverse drug reaction
nonsteroid antiinflammatory agent: CT, clinical trial
nonsteroid antiinflammatory agent: CB, drug combination
nonsteroid antiinflammatory agent: IT, drug interaction
nonsteroid antiinflammatory agent: IG, intragastric drug administration
nonsteroid antiinflammatory agent: DO, drug dose
nonsteroid antiinflammatory agent: CM, drug comparison
nonsteroid antiinflammatory agent: PO, oral drug administration
nitric oxide naproxen: DT, drug therapy
nitric oxide naproxen: PD, pharmacology
nitric oxide naproxen: CM, drug comparison
nitric oxide naproxen: DO, drug dose
nitric oxide naproxen: PO, oral drug administration
nitric oxide naproxen: CR, drug concentration
naproxen: DT, drug therapy
naproxen: PD, pharmacology
naproxen: CM, drug comparison

CONTROLLED TERM: Drug Descriptors:
naproxen: DO, drug dose
naproxen: PO, oral drug administration
naproxen: CR, drug concentration
acetylsalicylic acid 3 (nitroxymethyl)phenyl ester: DT, drug therapy
acetylsalicylic acid 3 (nitroxymethyl)phenyl ester: PD, pharmacology
acetylsalicylic acid 3 (nitroxymethyl)phenyl ester: AE, adverse drug reaction
acetylsalicylic acid 3 (nitroxymethyl)phenyl ester: CB, drug combination
acetylsalicylic acid 3 (nitroxymethyl)phenyl ester: CM, drug comparison
acetylsalicylic acid 3 (nitroxymethyl)phenyl ester: CT, clinical trial
acetylsalicylic acid 3 (nitroxymethyl)phenyl ester: IT, drug interaction

celecoxib: DT, drug therapy
celecoxib: PD, pharmacology
celecoxib: AE, adverse drug reaction
celecoxib: CB, drug combination
celecoxib: IT, drug interaction
celecoxib: CM, drug comparison
celecoxib: CT, clinical trial
cs 706: DT, drug therapy
cs 706: PD, pharmacology
cs 706: DO, drug dose
cs 706: CM, drug comparison
cs 706: PO, oral drug administration
benatoprazole: DT, drug therapy
benatoprazole: PD, pharmacology
benatoprazole: CT, clinical trial
benatoprazole: DO, drug dose
benatoprazole: PO, oral drug administration
benatoprazole: PK, pharmacokinetics
benatoprazole: CR, drug concentration
vancomycin: DT, drug therapy
vancomycin: PD, pharmacology
vancomycin: PE, pharmacoeconomics
vancomycin: CM, drug comparison
metronidazole: DT, drug therapy
metronidazole: AE, adverse drug reaction
rifalazil: DT, drug therapy
rifalazil: PD, pharmacology
rifalazil: PO, oral drug administration
rifalazil: CM, drug comparison
placebo
unclassified drug
azd 3582
r 109339

CAS REGISTRY NO.: (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (indometacin) 53-86-1, 74252-25-8, 7681-54-1; (naproxen) 22204-53-1, 26159-34-2; (acetylsalicylic acid 3 (nitroxymethyl)phenyl ester) 190442-10-5; (celecoxib) 169590-42-5; (benatoprazole) 113712-98-4; (vancomycin) 1404-90-6, 1404-93-9; (metronidazole) 39322-38-8, 443-48-1; (**rifalazil**) **129791-92-0**

CHEMICAL NAME: (1) Azd 3582; (2) Azd 3582; (3) Ncx 4016; (4) Cs 706; (5) R 109339; (6) Protop; (7) Protop; **(8) Krm 1648**; Aspirin

COMPANY NAME: (1) Astra Zeneca; (3) Nicox; (5) Sankyo; (6) Mitsubishi; (7) Hokuriku; (8) Activbiotics; Kyoto Prefectural University

L166 ANSWER 12 OF 40 EMBASE

ACCESSION NUMBER: 2004280709 EMBASE

TITLE: Advances in the management of Chlamydia pneumoniae infections.

AUTHOR: Hammerschlag M.R.

CORPORATE SOURCE: M.R. Hammerschlag, SUNY Downstate Medical Center, Department of Pediatrics/Medicine, Div. of Pediatric Infect. Diseases, Brooklyn, NY 11203-2098, United States. mhammerschlag@pol.net

SOURCE: Expert Review of Anti-Infective Therapy, (2003) Vol. 1, No. 3, pp. 493-503. .

Refs: 76
ISSN: 1478-7210 CODEN: ERATCK
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040722
Last Updated on STN: 20040722

ABSTRACT: One of the major characteristics of Chlamydia spp. is its ability to cause prolonged, often subclinical infections. Chronic, persistent infection with Chlamydia pneumoniae has been implicated in the pathogenesis of several chronic diseases initially not thought to be infectious, including asthma, arthritis and **atherosclerosis.** C. pneumoniae is susceptible in vitro to a wide range of antimicrobial agents that target either protein or DNA synthesis, including macrolides, ketolides, tetracyclines, quinolones and rifamycins. Practically all treatment studies evaluating presented or published to date have used serology alone for diagnosis of C. pneumonide infection, which only provides a clinical end point. The results of several treatment studies that did perform culture found that erythromycin, azithromycin (Zithromax®), clarithromycin (Biaxin®), levofloxacin (Levaquin®) and moxifloxacin (Avelox®) had a 70 to 90% efficacy in eradicating C. pneumoniae from the respiratory tract of children and adults with pneumonia. Persistence of the organism does not appear to be due to the development of antibiotic resistance. However, one cannot extrapolate from this experience to the treatment of chronic C. pneumoniae infection, especially ***cardiovascular*** disease. As there are no reliable serologic markers for chronic or persistent C. pneumoniae infection, it cannot be determined who is infected and who is not, which means that it cannot be assumed that any effect seen is due to successful treatment or eradication of C. pneumoniae.

CONTROLLED TERM: Medical Descriptors:
*chlamydiasis: DT, drug therapy
*Chlamydophila pneumoniae
persistent infection: DT, drug therapy
pathogenesis
asthma: CO, complication
arthritis: CO, complication
atherosclerosis: CO, complication
antibiotic sensitivity
in vitro study
drug targeting
DNA synthesis
serology
bacterium culture
drug efficacy
eradication therapy
respiratory system
bacterial pneumonia: DT, drug therapy
antibiotic resistance
cardiovascular disease: CO, complication
disease marker
treatment outcome
drug blood level
lung fluid
human
clinical trial
review

Drug Descriptors:
macrolide: CM, drug comparison
ketolide: CM, drug comparison
tetracycline derivative: CM, drug comparison
quinoline derived antiinfective agent: CM, drug comparison
rifamycin derivative: CM, drug comparison
erythromycin: CB, drug combination
erythromycin: CM, drug comparison
erythromycin: DT, drug therapy
azithromycin: CM, drug comparison
azithromycin: CR, drug concentration
azithromycin: DT, drug therapy
clarithromycin: CT, clinical trial
clarithromycin: CM, drug comparison
clarithromycin: CR, drug concentration
clarithromycin: DT, drug therapy
levofloxacin: CM, drug comparison
levofloxacin: CR, drug concentration
levofloxacin: DT, drug therapy
moxifloxacin: CM, drug comparison
moxifloxacin: DT, drug therapy
ofloxacin: CM, drug comparison
ofloxacin: CR, drug concentration
ofloxacin: DT, drug therapy
gemifloxacin: CM, drug comparison
gemifloxacin: CR, drug concentration
gemifloxacin: DT, drug therapy
doxycycline: CB, drug combination
doxycycline: CM, drug comparison
doxycycline: DT, drug therapy
tigecycline: CM, drug comparison
roxithromycin: CM, drug comparison
telithromycin: CM, drug comparison
11 amino 11 deoxy 5 o desosaminyl 3 oxo 6 o [3 (3 quinolyl)allyl]erythronolide a 11,12 cyclic carbamate: CM, drug comparison
11 amino 11 deoxy 5 o desosaminyl 3 oxo 6 o [3 (3 quinolyl)allyl]erythronolide a 11,12 cyclic carbamate: DT, drug therapy
11 amino 11 deoxy 5 o desosaminyl 3 oxo 6 o [3 (3 quinolyl)allyl]erythronolide a 11,12 cyclic carbamate: PO, oral drug administration
cethromycin: CM, drug comparison
cethromycin: DT, drug therapy
cethromycin: PO, oral drug administration
ciprofloxacin: CM, drug comparison
gatifloxacin: CM, drug comparison
rifampicin: CM, drug comparison
rifalazil: CM, drug comparison
trimethoprim: CM, drug comparison
sulfamethoxazole: CM, drug comparison
sparfloxacin: CM, drug comparison
garenoxacin: CM, drug comparison
ceftriaxone: CB, drug combination
ceftriaxone: CM, drug comparison
ceftriaxone: DT, drug therapy
cefuroxime axetil: CB, drug combination
cefuroxime axetil: CM, drug comparison
cefuroxime axetil: DT, drug therapy
cephalosporin: CM, drug comparison

cephalosporin: DT, drug therapy
unindexed drug
unclassified drug

CAS REGISTRY NO.: (erythromycin) 114-07-8, 70536-18-4; (azithromycin) 83905-01-5; (clarithromycin) 81103-11-9; (levofloxacin) 100986-85-4, 138199-71-0; (moxifloxacin) 151096-09-2; (ofloxacin) 82419-36-1; (gemifloxacin) 175463-14-6, 204519-65-3, 210353-53-0, 210353-55-2, 210353-56-3; (doxycycline) 10592-13-9, 17086-28-1, 564-25-0; (tigecycline) 220620-09-7; (roxithromycin) 80214-83-1; (telithromycin) 173838-31-8; (11 amino 11 deoxy 5 o desosaminyl 3 oxo 6 o [3 (3 quinolyl)allyl]erythronolide a 11,12 cyclic carbamate) 205110-48-1; (ciprofloxacin) 85721-33-1; (gatifloxacin) 112811-59-3, 180200-66-2; (rifampicin) 13292-46-1; (**rifalazil**) **129791-92-0**; (trimethoprim) 738-70-5; (sulfamethoxazole) 723-46-6; (sparfloxacin) 111542-93-9; (garenoxacin) 194804-75-6, 223652-82-2, 223652-90-2; (ceftriaxone) 73384-59-5, 74578-69-1; (cefuroxime axetil) 64544-07-6; (cephalosporin) 11111-12-9

CHEMICAL NAME: (1) Zithromax; (2) Biaxin; (3) Levaquin; (4) Factive; (5) Zagam; (6) Avelox; (7) Tequin; (8) Rocephin; Abt 773

COMPANY NAME: (1) Pfizer (United States); (2) Abbott (United States); (3) Johnson and Johnson (United States); (4) GeneSoft; (5) Rhone Poulenc Rorer (United States); (6) Bayer (United States); (7) Bristol Myers Squibb (United States); (8) Hoffmann La Roche (United States); Ranbaxy (United States)

L166 ANSWER 13 OF 40 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001197861 EMBASE

TITLE: Profiles of expression of the therapeutic efficacy of **KRM-1648** in mice infected with Mycobacterium avium complex at different challenge doses.

AUTHOR: Shimizu T.; Ogasawara K.; Sato K.; Sano C.; Tomioka H.

CORPORATE SOURCE: T. Shimizu, Department of Microbiology, Shimane Medical University, Shimane 693-8501, Japan

SOURCE: Kekkaku, (2001) Vol. 76, No. 5, pp. 413-418. .
Refs: 12
ISSN: 0022-9776 CODEN: KEKKAG

COUNTRY: Japan

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 004 Microbiology
037 Drug Literature Index

LANGUAGE: Japanese

SUMMARY LANGUAGE: English; Japanese

ENTRY DATE: Entered STN: 20010622
Last Updated on STN: 20010622

ABSTRACT: Studied were made on the profiles of the therapeutic efficacy of ***KRM*** **-1648** (KRM) against Mycobacterium avium complex (MAC) infection, which was induced in mice at different challenge doses, in reducing bacterial growth in the visceral organs and altering the profiles of cytokine mRNA expression at the sites of infection. First, bacterial growth in the lungs of mice infected with either high or low challenge doses of MAC, was reduced due to KRM treatment. This effect was noted even in the early phase of infection (week 4) in mice, that were given a high-dose infection. Second, marked therapeutic efficacy of KRM was observed in mice, that were given low-dose MAC infection, in terms of the reduction in bacterial loads in the spleen. However, in mice given a high-dose bacterial challenge, KRM did not exhibit such an efficacy. Third, the expression of both proinflammatory

cytokines (TNF- α, IFN- γ) and anti-inflammatory cytokines (IL-10, TGF- β) in mRNA levels were increased at 4 weeks after infection. Notably, all of the cytokines tested for the mRNA expression levels were higher in mice given a low-dose MAC infection as compared to those in mice given a high-dose infection. KRM treatment increased the mRNA levels of these cytokines at week 4, while TGF- β mRNA expression at week 8 was conversely decreased by KRM treatment. These findings suggest that the profiles of the therapeutic efficacy of KRM vary in mice given low- or high-dose MAC infection.

CONTROLLED TERM: Medical Descriptors:
*mycobacteriosis: ET, etiology
*Mycobacterium intracellulare avium
drug efficacy
cytokine release
bacterial growth
spleen
nonhuman
mouse
animal experiment
animal model
controlled study
article
Drug Descriptors:
***rifalazil**
*cytokine: EC, endogenous compound
*messenger RNA: EC, endogenous compound
tumor necrosis factor alpha: EC, endogenous compound
gamma interferon: EC, endogenous compound
interleukin 10: EC, endogenous compound
transforming growth factor beta: EC, endogenous compound

CAS REGISTRY NO.: (**rifalazil**) **129791-92-0**; (gamma interferon) 82115-62-6

CHEMICAL NAME: **Krm 1648**

L166 ANSWER 14 OF 40 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 1999100147 EMBASE

TITLE: The modulating effects of proinflammatory cytokines interferon-gamma (IFN-γ) and tumour **necrosis** factor-alpha (TNF-α), and immunoregulating cytokines IL-10 and transforming growth factor-beta (tgf-β), on anti- microbial activity of murine peritoneal macrophages against Mycobacterium avium-intracellulare complex.

AUTHOR: Sano C.; Sato K.; Shimizu T.; Kajitani H.; Kawauchi H.; Tomioka H.

CORPORATE SOURCE: Dr. H. Tomioka, Dept. of Microbiology and Immunology, Shimane Medical University, Izumo, Shimane 693-8501, Japan. tomioka@shimane-med.ac.jp

SOURCE: Clinical and Experimental Immunology, (1999) Vol. 115, No. 3, pp. 435-442. .
Refs: 40
ISSN: 0009-9104 CODEN: CEXIAL

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 004 Microbiology
006 Internal Medicine
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19990419
Last Updated on STN: 19990419

ABSTRACT: We assessed the roles of proinflammatory cytokines IFN-γ and TNF-α, and immunoregulatory cytokines IL-10 and TGF-β in the modulation of the anti-microbial activity of murine peritoneal macrophages against Mycobacterium avium-intracellulare complex (MAIC). First, both IFN-γ and TNF-α significantly reduced the bacterial growth in macrophages, indicating that these cytokines participate in up-regulation of macrophage anti-MAIC function. Second, although MAIC-infected macrophages produced substantial amounts of IL-10 and TGF-β, neutralization of endogenous IL-10 and TGF-β with anti-IL-10 and anti-TGF-β antibodies, respectively, did not affect the intracellular growth of MAIC in macrophages from mice with Bcg(s) (MAIC- susceptible) or Bcg(r) (MAIC-resistant) genotype, regardless of the virulence of test MAIC strains. The same result was also obtained for macrophages stimulated with IFN-γ or TNF-α. Third, in MAIC-infected mice, the growth of organisms at the sites of infection (lungs and spleens) was not affected by administration of anti-IL-10 or anti-TGF-β antibodies. These findings indicate that, in the case of mice, endogenous IL-10 and TGF-β are essentially ineffective in down-regulating macrophage anti-MAIC functions not only in vitro but also in vivo.

CONTROLLED TERM: Medical Descriptors:
*immunostimulation
*mycobacterium intracellulare avium
*mycobacteriosis: DT, drug therapy
peritoneum macrophage
bacteriostasis
drug efficacy
drug mechanism
bacterial growth
macrophage activation
cytokine release
bacterial virulence
antigen binding
dose time effect relation
protein determination
nonhuman
female
mouse
animal experiment
animal model
controlled study
animal cell
oral drug administration
intravenous drug administration
intraperitoneal drug administration
article
priority journal
Drug Descriptors:
*cytokine: DV, drug development
*cytokine: DO, drug dose
*cytokine: DT, drug therapy
*cytokine: PD, pharmacology
*recombinant gamma interferon: DV, drug development
*recombinant gamma interferon: DO, drug dose
*recombinant gamma interferon: DT, drug therapy
*recombinant gamma interferon: PD, pharmacology
***recombinant tumor necrosis factor alpha: DV, drug**

development
***recombinant tumor necrosis factor alpha: DO, drug dose**
***recombinant tumor necrosis factor alpha: DT, drug therapy**
***recombinant tumor necrosis factor alpha: PD, pharmacology**
*interleukin 10 antibody: DV, drug development
*interleukin 10 antibody: DO, drug dose
*interleukin 10 antibody: DT, drug therapy
*interleukin 10 antibody: PD, pharmacology
*cytokine antibody: DV, drug development
*cytokine antibody: DO, drug dose
*cytokine antibody: DT, drug therapy
*cytokine antibody: PD, pharmacology
*transforming growth factor beta antibody: DV, drug development
*transforming growth factor beta antibody: DO, drug dose
*transforming growth factor beta antibody: DT, drug therapy
*transforming growth factor beta antibody: PD, pharmacology
interleukin 10: EC, endogenous compound
transforming growth factor beta: EC, endogenous compound
3' hydroxy 5' (4 isobutyl 1 piperazinyl)benzoxazinorifamycin: DV, drug development
3' hydroxy 5' (4 isobutyl 1 piperazinyl)benzoxazinorifamycin: DO, drug dose
3' hydroxy 5' (4 isobutyl 1 piperazinyl)benzoxazinorifamycin: DT, drug therapy
3' hydroxy 5' (4 isobutyl 1 piperazinyl)benzoxazinorifamycin: PD, pharmacology

CAS REGISTRY NO.: (3' hydroxy 5' (4 isobutyl 1 piperazinyl)benzoxazinorifamycin) **129791-92-0**
COMPANY NAME: Genzyme (United States)

L166 ANSWER 15 OF 40 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 97365928 EMBASE
DOCUMENT NUMBER: 1997365928
TITLE: Basic and clinical studies on pathogenesis of pulmonary Mycobacterium avium complex disease.
AUTHOR: Suzuki K.
CORPORATE SOURCE: K. Suzuki, Department of Infection/Inflammation, Chest Disease Research Institute, Kyoto University, Sakyo-ku, Kyoto 606, Japan
SOURCE: Kekkaku, (1997) Vol. 72, No. 10, pp. 579-585. .
Refs: 8
ISSN: 0022-9776 CODEN: KEKKAG
COUNTRY: Japan
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 004 Microbiology
005 General Pathology and Pathological Anatomy
015 Chest Diseases, Thoracic Surgery and Tuberculosis
030 Pharmacology
037 Drug Literature Index
LANGUAGE: Japanese
SUMMARY LANGUAGE: English; Japanese
ENTRY DATE: Entered STN: 971212
Last Updated on STN: 971212
ABSTRACT: I have studied pathogenesis of pulmonary Mycobacterium avium complex disease (PMAC), using mouse and human alveolar macrophage (PAM) model of the

infection as well as clinical evaluations. The mouse model revealed no relation between natural resistance against the bacteria and the activation of macrophages which was evaluated on the basis of releasing capacities of prostaglandin E2 and superoxide anion. The PAM model suggested that TNF-α and GM-CSF could activate PAM to restrict the intracellular growth of the bacteria, probably not through the superoxide anion release, but through the myeloperoxidase-halide system. It was also found that rifamycins in combination with clarithromycin could have a good bactericidal effect in the PAM-model of the infection. Clinical evaluations suggested that defect in local pulmonary disease, such as healed pulmonary tuberculous lesions, pneumoconiosis, and COPD was more important predisposing factor than defect in systemic defense in the development of PMAC. Most patients having PMAC without predisposing factors are elderly women, the reason of which is the most important question to be answered in the future studies.

CONTROLLED TERM: Medical Descriptors:
*lung infection: ET, etiology
*lung infection: DI, diagnosis
*lung infection: DT, drug therapy
*mycobacteriosis: DI, diagnosis
*mycobacteriosis: ET, etiology
*mycobacteriosis: DT, drug therapy
animal model
bacterial growth
chronic obstructive lung disease
clinical examination
conference paper
disease predisposition
female
human
lung alveolus macrophage
lung tuberculosis
male
mouse
mycobacterium intracellulare avium
nonhuman
pathogenesis
pneumoconiosis
sex difference
Drug Descriptors:
*3' hydroxy 5' (4 isobutyl 1 piperazinyl)benzoxazinorifamycin: CB, drug combination
*3' hydroxy 5' (4 isobutyl 1 piperazinyl)benzoxazinorifamycin: DT, drug therapy
*clarithromycin: CB, drug combination
*clarithromycin: DT, drug therapy
*rifabutin: CB, drug combination
*rifabutin: DT, drug therapy
granulocyte macrophage colony stimulating factor: EC, endogenous compound
prostaglandin e2: EC, endogenous compound
superoxide: EC, endogenous compound
tumor necrosis factor alpha: EC, endogenous compound

CAS REGISTRY NO.: (3' hydroxy 5' (4 isobutyl 1 piperazinyl)benzoxazinorifamycin) **129791-92-0**; (clarithromycin) 81103-11-9; (rifabutin) 72559-06-9; (prostaglandin e2) 363-24-6; (superoxide) 11062-77-4

CHEMICAL NAME: **Krm 1648**

L166 ANSWER 16 OF 40 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 96011498 EMBASE
DOCUMENT NUMBER: 1996011498
TITLE: Mechanism of bacterial regrowth at the sites of infection in Mycobacterium avium complex-infected mice during treatment with chemotherapeutic agents.
AUTHOR: Sato K.; Tomioka H.; Win Win Maw; Saito H.
CORPORATE SOURCE: Dept. of Microbiology and Immunology, Shimane Medical University,Izumo 693, Japan
SOURCE: Kekkaku, (1995) Vol. 70, No. 12, pp. 673-678. .
ISSN: 0022-9776 CODEN: KEKKAG
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
037 Drug Literature Index
LANGUAGE: Japanese
SUMMARY LANGUAGE: English; Japanese
ENTRY DATE: Entered STN: 960130
Last Updated on STN: 960130

ABSTRACT: Although various antimicrobial drugs show appreciable bactericidal activity in the early phase (2 to 4 weeks after infection) of Mycobacterium avium complex (MAC) infections in mice, no drug, as far as we known, can continue to exert the growth inhibiting activity against the bacteria at the site of infection in the progressed stage. Here, we studied the mechanisms of the bacterial regrowth which usually starts around 2-4 weeks after infection. First, the changes in the level of TNF-α, IFN-γ, IL-6 and IL-10 in the lungs and spleen during the course of MAC infections was examined. Tissue levels of TNF α and IL-10 increased around weeks 2 to 4, then rapidly decreased thereafter, and returned to the normal levels by week 8, while levels of IFN-γ and IL-6 remained very low throughout the observation period. In this experiment, the bacterial CFUs rapidly decreased during the first 2 weeks of the treatment with a rifamycin derivative, **KRM-1648**, and thereafter the regrowth of the organisms was observed even in mice treated continuously with **KRM-1648**, although the rate of bacterial growth in the treated mice was much lower than in untreated control mice. Second, effect of either anti-TGF-β or anti-IL-10 antibody on intracellular growth of MAC in human monocytes cultured in vitro in the medium with or without addition of TNF-α or IFN-γ were examined. Anti-TGF-β and anti-IL-10 antibodies potently reduced the bacterial growth in monocytes. Effects of TNF-α and IFN-γ in reducing the bacterial growth was potentiated by the addition of either anti-TGF-β of anti-IL-10 antibody. Third, anti-IL-10 antibody augmented to some extent the chemotherapeutic efficacy of **KRM 1648** against MAC infection, when the drug was given to mice at weeks 2 and 4 after infection. From these results, it is suggested that IL-10 derived from MAC infected macrophages in response to stimulation with some bacterial components, such as lipoarabinomanian, might downregulate the antimicrobial function of host macrophages against MAC.

CONTROLLED TERM: Medical Descriptors:
*antimicrobial therapy
*tuberculosis: ET, etiology
*tuberculosis: EP, epidemiology
*tuberculosis: DT, drug therapy
*tuberculosis: DI, diagnosis
animal experiment
animal model
article
bacterial growth

colony forming unit
controlled study
down regulation
macrophage function
microbial growth
mouse
mycobacterium intracellulare avium
nonhuman
tissue level
Drug Descriptors:
*rifamycin derivative: DT, drug therapy
gamma interferon
interleukin 10
interleukin 6
3' hydroxy 5' (4 isobutyl 1 piperazinyl)benzoxazinorifamycin
tumor necrosis factor alpha
CAS REGISTRY NO.: (gamma interferon) 82115-62-6; (3' hydroxy 5' (4 isobutyl 1 piperazinyl)benzoxazinorifamycin) **129791-92-0**
CHEMICAL NAME: **Krm 1648**

L166 ANSWER 17 OF 40 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 94159375 EMBASE
DOCUMENT NUMBER: 1994159375
TITLE: Contributions of animal and macrophage models to the understanding of host parasite interaction of Mycobacterium avium complex (MAC) disease.
AUTHOR: Gangadharam P.R.J.; Reddy M.V.
CORPORATE SOURCE: Mycobacteriology Research Laboratory, University of Illinois, College of Medicine,Chicago, IL 60612, United States
SOURCE: Research in Microbiology, (1994) Vol. 145, No. 3, pp. 214-224. .
ISSN: 0923-2508 CODEN: RMCREW
COUNTRY: France
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 004 Microbiology
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 940622
Last Updated on STN: 940622
CONTROLLED TERM: Medical Descriptors:
*bacterial infection: DT, drug therapy
*host parasite interaction
*mycobacterium avium
animal cell
animal model
conference paper
human
human cell
macrophage
nonhuman
priority journal
Drug Descriptors:
*antibiotic agent: DT, drug therapy
*cytokine: DT, drug therapy
6 cyclooctylamino 5,8 quinolinedione: DT, drug therapy
amikacin: DT, drug therapy
calcitriol: DT, drug therapy

clarithromycin: DT, drug therapy
clofazimine: DT, drug therapy
colony stimulating factor 1: DT, drug therapy
ethambutol: DT, drug therapy
gamma interferon: DT, drug therapy
gentamicin: DT, drug therapy
granulocyte macrophage colony stimulating factor: DT, drug therapy
interleukin 1alpha: DT, drug therapy
interleukin 2: DT, drug therapy
interleukin 4: DT, drug therapy
interleukin 6: DT, drug therapy
3' hydroxy 5' (4 isobutyl 1 piperazinyl)benzoxazinorifamycin: DT, drug therapy
liposome: DT, drug therapy
rifabutin: DT, drug therapy
streptomycin: DT, drug therapy
tumor necrosis factor: DT, drug therapy
tumor necrosis factor alpha: DT, drug therapy

CAS REGISTRY NO.: (6 cyclooctylamino 5,8 quinolinedione) 35961-95-6; (amikacin) 37517-28-5, 39831-55-5; (calcitriol) 32222-06-3, 32511-63-0, 66772-14-3; (clarithromycin) 81103-11-9; (clofazimine) 2030-63-9; (colony stimulating factor 1) 81627-83-0; (ethambutol) 10054-05-4, 1070-11-7, 3577-94-4, 74-55-5; (gamma interferon) 82115-62-6; (gentamicin) 1392-48-9, 1403-66-3, 1405-41-0; (interleukin 2) 85898-30-2; (3' hydroxy 5' (4 isobutyl 1 piperazinyl)benzoxazinorifamycin) **129791-92-0**; (rifabutin) 72559-06-9; (streptomycin) 57-92-1

CHEMICAL NAME: **Krm 1648**

L166 ANSWER 18 OF 40 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:33069 BIOSIS
DOCUMENT NUMBER: PREV200400034265
TITLE: **Rifalazil**, a novel benzoxazinorifamycin, is active against Chlamydia pneumoniae and reduces transmission of chlamydial infection from monocytes to endothelium.
AUTHOR(S): Rupp, J. [Reprint Author]; Hellberg, A. [Reprint Author]; Rothstein, D.; Maass, M. [Reprint Author]
CORPORATE SOURCE: Med. Microbiol., Univ. of Luebeck, Luebeck, Germany
SOURCE: Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, (2003) Vol. 43, pp. 208. print. Meeting Info.: 43rd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, IL, USA. September 14-17, 2003. American Society for Microbiology.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Jan 2004
Last Updated on STN: 7 Jan 2004

ABSTRACT:Background: Chlamydia pneumoniae (CP) causes acute respiratory infections, is disseminated by blood monocytes (PBMC), and persists in ***atherosclerotic*** lesions. In PBMC CP enters a viable persistent state, which is not completely eradicable by antibiotics. We evaluated the in vitro activity of **rifalazil**, a novel benzoxazinorifamycin, in acute chlamydial infection of respiratory cells. In addition, we analysed drug effects on the transmission of chronic infection from PBMC to endothelial cells in a co-culture model. Methods: MICs of **rifalazil** (ActivBiotics,

Lexington MA), rifampin and azithromycin were tested in a standardized system of acute infection in HEp-2 cells for 16 vascular and respiratory CP strains. Emergence of resistance was monitored in 20 serial passages under subinhibitory drug concentrations. Transmission of CP infection from human PBMC to human ***coronary*** endothelial cells was compared in a co-culture system with ***rifalazil*** , rifampin or azithromycin added at serum peak concentrations. Spread of infection was observed by immunofluorescence microscopy. Results: MIC90 for **Rifalazil**: 0.00025 mg/l, rifampin: 0.005 mg/l, azithromycin: 0.08 mg/l. Resistance did not emerge. **Rifalazil** reduced transmission of chlamydial infection from PBMC to endothelium after 120 h by 44%, azithromycin by 12%, rifampin was toxic for the endothelium. Conclusions: **Rifalazil** was highly active against CP in vitro and did not induce resistance. In a novel functional assay on the spread of chronic CP infection by cell to cell contact, **rifalazil** significantly reduced transmission of CP from PBMC to endothelium in comparison to azithromycin. ***Rifalazil*** appears efficient in eradicating acute CP infection and may be of potential benefit in the prevention of PBMC-mediated systemic dissemination of the pathogen.

CONCEPT CODE:
General biology - Symposia, transactions and proceedings 00520
Cytology - General 02502
Cytology - Animal 02506
Cytology - Human 02508
Pathology - Therapy 12512
Cardiovascular system - Physiology and biochemistry 14504
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Morphology and cytology of bacteria 30500
Physiology and biochemistry of bacteria 31000
Immunology - General and methods 34502
Medical and clinical microbiology - Bacteriology 36002
Chemotherapy - General, methods and metabolism 38502
Chemotherapy - Antibacterial agents 38504

INDEX TERMS:
Major Concepts
Cell Biology; Immune System (Chemical Coordination and Homeostasis); Infection; Pharmacology

INDEX TERMS:
Parts, Structures, & Systems of Organisms
coronary endothelial cell: circulatory system; endothelium; monocyte: blood and lymphatics, immune system; peripheral blood mononuclear cell: blood and lymphatics, immune system

INDEX TERMS:
Diseases
Chlamydia pneumoniae infection: bacterial disease
Chlamydia Infections (MeSH)

INDEX TERMS:
Chemicals & Biochemicals
rifalazil: antibacterial-drug, antiinfective-drug, benzoxazinorifamycin

ORGANISM:
Classifier
Chlamydiaceae 07121
Super Taxa
Chlamydiales; Rickettsias and Chlamydias; Eubacteria; Bacteria; Microorganisms
Organism Name
Chlamydia pneumoniae (species): pathogen
Taxa Notes
Bacteria, Eubacteria, Microorganisms

ORGANISM:
Classifier
Hominidae 86215

Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
HEp-2 (cell line)
human (common): host
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
REGISTRY NUMBER: **129791-92-0 (rifalazil)**

L166 ANSWER 19 OF 40 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:265553 BIOSIS
DOCUMENT NUMBER: PREV200300265553
TITLE: Antimicrobial activity of RifalazilTM for Chlamydia pneumoniae.
AUTHOR(S): Mahony, J. B. [Reprint Author]; Song, X.
CORPORATE SOURCE: McMaster University, St. Joseph's Healthcare, Hamilton, ON, Canada
SOURCE: Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, (2002) Vol. 42, pp. 165. print.
Meeting Info.: 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy. San Diego, CA, USA. September 27-30, 2002. American Society for Microbiology.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Jun 2003
Last Updated on STN: 4 Jun 2003
ABSTRACT:Background: C. pneumoniae is a common cause of pharyngitis and pneumonia. Epidemiological studies have established an association between C. pneumnoniae infection and **coronary artery** disease. We have evaluated a new rifamycin derivative, RifalazilTM for antichlamydial activity and evaluated its effect on chlamydial gene expression. Methods: MIC90 for RifalazilTM (ActivBiotics, Cambridge; MA), Doxycycline, Metronidazole and Isoniazid were determined for C. pneumoniae using HEp-2 cells and staining inclusions at 72 hr using FITC-conjugated anti-LPS monoclonal antibody. Transcription of 6 key chlamydial genes (ompA, hsp60, parB, hctA, ftsK, and 16S RNA) was measured at 24, 48, and 72 hr post infection by RT-PCR. Results: MIC90 for C. pneumoniae were as follows: RifalazilTM, 0.0002 ug/mL, Doxycycline, 0.2 ug/mL, Metronidazole, 800 ug/mL, and Isoniazid, 400 ug/mL. Synergism between either Metronidazole or Isoniazid and RifalazilTM was unremarkable; Metronidazole (200-400 ug/mL) and Isoniazid (200-400 ug/mL) reduced the MIC90 for RifalazilTM by 2-4 fold. Both RifalazilTM (0.0008 ug/mL) and Doxycycline (1 ug/mL) abolished the expression of key chlamydial genes involved in chromosomal condensation and partitioning (hctA, par B), and cytokinesis (ftsK) and downregulated expression of genes coding for the major outer membrane protein (ompA) and heat shock protein (hsp60) by 90%. Transcripts for 16S RNA were not affected by either Doxycycline or RifalazilTM. Consclusions: RifalazilTM has the lowest MIC90 for C. pneumoniae (0.0002 ug/mL) of all previously reported antibiotics. The mechanism of inhibition appears to be at the transcriptional level turning off essential genes required for cell division. Due to its potent antichlamydial activity, RifalazilTM may offer advantages over other antibiotics in the treatment of persistent chlamydial infections and may reduce the inflammation asssociated with C. pneumoniae infection by downregulating hsp60 expression.
CONCEPT CODE: General biology - Symposia, transactions and proceedings 00520
Biochemistry studies - General 10060
Pathology - Therapy 12512

Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Physiology and biochemistry of bacteria 31000
Chemotherapy - General, methods and metabolism 38502
Chemotherapy - Antibacterial agents 38504

INDEX TERMS: Major Concepts
Infection; Pharmacology

INDEX TERMS: Chemicals & Biochemicals
doxycycline: antibacterial-drug, antiinfective-drug;
isoniazid: antibacterial-drug, antiinfective-drug;
metronidazole: antibacterial-drug, antiinfective-drug;
rifalazil: antibacterial-drug,
antiinfective-drug, antimicrobial activity, minimum
inhibitory concentration

ORGANISM: Classifier
Chlamydiaceae 07121
Super Taxa
Chlamydiales; Rickettsias and Chlamydias; Eubacteria;
Bacteria; Microorganisms
Organism Name
Chlamydia pneumoniae (species): pathogen
Taxa Notes
Bacteria, Eubacteria, Microorganisms

ORGANISM: Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
HEp-2 cell line (cell line): human hepatoma cells
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates,
Vertebrates

REGISTRY NUMBER: 564-25-0 (doxycycline)
54-85-3 (isoniazid)
443-48-1 (metronidazole)
129791-92-0 (rifalazil)

L166 ANSWER 20 OF 40 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2001:458862 BIOSIS
DOCUMENT NUMBER: PREV200100458862
TITLE: Profiles of expression of the therapeutic efficacy of **KRM-1648** and clarithromycin in mice infected with Mycobacterium avium complex at different challenge doses.
AUTHOR(S): Sato, K. [Reprint author]; Ogasawara, K. [Reprint author]; Shimizu, T. [Reprint author]; Akashi, T.; Sano, C. [Reprint author]; Tomioka, H. [Reprint author]
CORPORATE SOURCE: Shimane Medical University, Izumo, Japan
SOURCE: International Journal of Antimicrobial Agents, (June, 2001) Vol. 17, No. Supplement 1, pp. S45-S46. print.
Meeting Info.: 22nd International Congress of Chemotherapy. Amsterdam, Netherlands. June 30-July 03, 2001.
ISSN: 0924-8579.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Sep 2001
Last Updated on STN: 22 Feb 2002

CONCEPT CODE: General biology - Symposia, transactions and proceedings 00520
Biochemistry studies - General 10060
Pathology - Therapy 12512
Pharmacology - General 22002
Physiology and biochemistry of bacteria 31000
INDEX TERMS: Major Concepts
Infection; Pharmacology
INDEX TERMS: Parts, Structures, & Systems of Organisms
spleen: blood and lymphatics, immune system
INDEX TERMS: Diseases
Mycobacterium avium complex infection: bacterial disease
Mycobacterium avium-intracellulare Infection (MeSH)
INDEX TERMS: Chemicals & Biochemicals
IFN-alpha mRNA [interferon-alpha messenger RNA]: expression; IL-10 mRNA [interleukin-10 messenger RNA]: expression; **KRM-1648**: antibacterial-drug; TGF-alpha mRNA [transforming growth factor-alpha messenger RNA]: expression; TNF-alpha mRNA [tumor **necrosis** factor-alpha messenger RNA]: expression; clarithromycin: antibacterial-drug
INDEX TERMS: Methods & Equipment
challenge test: analytical method
INDEX TERMS: Miscellaneous Descriptors
expression profile; Meeting Poster; Meeting Abstract
ORGANISM: Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse: animal model, host
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
ORGANISM: Classifier
Mycobacteriaceae 08881
Super Taxa
Mycobacteria; Actinomycetes and Related Organisms; Eubacteria; Bacteria; Microorganisms
Organism Name
Mycobacterium avium complex: pathogen
Taxa Notes
Bacteria, Eubacteria, Microorganisms
REGISTRY NUMBER: **129791-92-0 (KRM-1648)**
81103-11-9 (clarithromycin)

L166 ANSWER 21 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2006:54662 USPATFULL
TITLE: Prodrugs containing novel bio-cleavable linkers
INVENTOR(S): Satyam, Apparao, Mumbai, INDIA

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2006046967	A1	20060302	
APPLICATION INFO.:	US 2005-213396	A1	20050826	(11)

NUMBER DATE

PRIORITY INFORMATION:	IN 2005-7792005	20050701
	US 2004-604632P	20040826 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	Sreenivasarao Vepachedu, 1230 Georgetown Way, Vernon Hills, IL, 60061, US	
NUMBER OF CLAIMS:	30	
EXEMPLARY CLAIM:	1	
LINE COUNT:	4813	

AB The invention provides the compounds of formula (I) or pharmaceutically acceptable salts thereof. The invention also provides pharmaceutical compositions comprising one or more compounds of formula I or intermediates thereof and one more of pharmaceutically acceptable carriers, vehicles or diluents. The invention further provides methods of preparation and methods of use of prodrugs including NO-releasing prodrugs, double prodrugs and mutual prodrugs comprising the compounds of formula I.

SUMM . . . as superoxide (O.sub.2.sup.-) to generate a nefarious peroxynitrite (ONOO.sup.-) molecule, which is implicated in many human diseases such as diabetes, **heart** disease, Alzheimer's disease and multiple sclerosis. In this setting, NO is often viewed as pathogenic. However, the chemistry of NO. . .

SUMM NO deficiency has been implicated in the genesis and evolution of several disease states. In patients with **cardiovascular** problems, the production of superoxide is increased and level or location of NO synthesis is disrupted thereby causing cellular dysfunction. . .

SUMM . . . the bioactivity or production of NO have been shown to improve endothelium-dependent vasodilation, reduce symptoms, and slow the progression of **atherosclerosis.** Some of the strategies for NO modulation encompass anti-inflammatory, sexual dysfunction, and **cardiovascular** indications. Apart from newly developed drugs, several commonly used **cardiovascular** drugs exert their beneficial action, at least in part, by modulating the NO pathway. Pharmacological compounds that release NO have been useful tools for evaluating the pivotal role of NO in **cardiovascular** physiology and therapeutics.

SUMM . . . release NO in solution. Some NO donors, such as isoamyl nitrite, nitroglycerine (GTN) and sodium nitroprusside, have been used in **cardiovascular** medicine long before their biochemical mechanism was understood. The common mode of action for these drugs is liberation of NO,. . . those that require enzymatic metabolism to generate NO. See, for example, Ignarro, L. J. et al., Nitric oxide donors and **cardiovascular** agents modulating the bioactivity of nitric oxide: an overview, Circ. Res. 2002, 90, 21-28.

SUMM Nitroglycerine/glycerine trinitrate (GTN) and compounds referred to as nitrovasodilators or NO donors are frequently used in the treatment of **ischemic heart** disease. The common mode of action for these drugs is liberation of NO, which evokes relaxation of smooth muscle through. . . activation of guanylate cyclase with subsequent formation of cGMP. However, early development of tolerance to nitrate therapy, particularly during acute **myocardial** infarction, has been the clinically significant drawback with GTN and some of the other available organic nitrates. This is a significant clinical problem and there exists a need for novel nitrate-based anti-**anginal** agents, which do not cause the problem of nitrate tolerance.

SUMM . . . drug molecule. Existing drugs from a large number of therapeutic areas such as anti-inflammatory, antiallergic, antibiotic,

anticancer, antidiabetic, antiviral, antihypertensive, **antianginal**, anticonvulsant, analgesic, antiasthmatic, antidepressant, antidiarrheal, antiinfective, antimigraine, antipsychotic, antipyratic, antiulcerative, antithrombotic, etc., were made and evaluated. Some of Nicox's patents. . .

DETD . . . a small group of closely related compounds. Prous Science is an international health science publishing company, established in 1958 and **headquartered** in Barcelona, Spain. Prous Science Drugs of the Future.TM., produced by Prous Science Publishers, contains comprehensive drug monographs providing product. . .

DETD . . . of the invention provides the use of the compounds of formula (I) in combination with a compound used to treat **cardiovascular** diseases selected from the group consisting of: beta adrenergic blockers, calcium channel blockers, angiotensin II receptor antagonists, antithrombotics, HMGCoA reductase. . .

DETD . . . the pharmaceutical compositions containing compounds of formula (I) in combination with a compound, used to treat other diseases such as **cardiovascular** diseases, selected from beta adrenergic blockers, calcium channel blockers, angiotensin II receptor antagonists, antithrombotics, HMGCoA reductase inhibitors, aspirin or nitrooxy. . .

DETD . . . of amlodipine (Pfizer's Norvasc®) and lisinopril (Zeneca's Zestril®) (I-AA-MPD2) is proposed as a potential treatment option for hypertension and congestive **heart** failure. Amlodipine is a calcium channel blocker and is used as an antihypertensive and **antianginal** agent. Lisinopril is an angiotensin-converting enzyme (ACE) inhibitor and is used for the treatment of hypertension and congestive **heart** failure. A combination therapy using these two drugs has been proven to be more effective treatment option than monotherapy using. . .

DETD . . . treatment option for mild to moderate hypertension. Amlodipine is a calcium channel blocker and is used as an antihypertensive and **antianginal** agent. Losartan potassium is an angiotensin II blocker and is used for the treatment of hypertension. A combination therapy using. . .

DETD . . . N4-beta-D-Glucosylsulfanilamide, Gramicidin(s), Isepamicin, Kanamycin(s), Lincomycin, Meclocycline, Methacycline, Micronomicin, Neomycin, Netilmicin, Novobiocin, Paromomycin, Phenyl aminosalicylate, Pipacycline, Polymyxin, Prinmycin, Ramoplanin, Ribostamycin, Rifabutin, **Rifalazil**, Rifamide, Rifamycin SV, Rifampin, Rifapentine, Rifaximin, Ristocetin, Salinazid, Sancycline, Sisomicin, Streptolydigin, Streptomycin, Streptonicozid, 2-p-Sulfanilylanilinoethanol, Thiamphenicol, Thiostrepton, Tobramycin, Tuberactinomycin, Viomycin, and. . .

DETD Anticancer, Antioxidative, Antiinflammatory, and **Cardioprotective** Agent:

DETD **Cardiovascular** System:

DETD Antiarrhythemic drugs, Antihypertensives (including alfa/beta-blockers, channel blockers, ACE inhibitors, Angiotensin II receptor antagonists, diuretics, etc.), **Antianginals** (includinig nitrates, calcium channel blockers, etc.), Drugs for **cardiac** failure and shock, Vasodilators, Coagulants, Anticoagulants, Thrombolytics and antiplatelet drugs.

DETD . . . the prodrugs and mutual prodrugs of anticonvulsants described in this invention were evaluated at National Institute of Neurological Disorders and **Stroke** (NINDS), National Institute of Health (NIH), under their Antiepileptic Screening Program (ASP).

DETD . . . tonic-clonic seizure and provides an indication of a compound's ability to prevent seizure spread when all neuronal circuits in the **brain** are maximally active. These seizures are highly reproducible and electro-physiologically consistent with human seizures.

For all tests based on MES. . .
CLM What is claimed is:
. . . diseases, aural preparations, nasal preparations, oropharyngeal preparations, Antiarrhythemic drugs, Antihypertensives, alfa/beta-blockers, channel blockers, ACE inhibitors, Angiotensin II receptor antagonists, diuretics, **Antianginals**, nitrates, calcium channel blockers. Drugs for **cardiac** failure and shock, Vasodilators, Coagulants, Anticoagulants, Thrombolytics, antiplatelet drugs, Respiratory stimulants, Antitissives, Expectorants, Mucolytics, Decongestants, Antihistamine agents, antiasthmatics; Antiulcer, Antisecretory. . .
. . . subject in need there of for prevention or treatment of diseases of Central Nervous System, Eye, Ear, Nose and Oropharyrnx, **Cardiovascular** System, Respiratory System, Gastrointestinal tract system, Genito-urinary system, skin, musculo-skeletal system, Endocrine system, metabolism and neoplastic disorders, infectious diseases, allergy. . .

L166 ANSWER 22 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2006:16288 USPATFULL
TITLE: Methods for preparing purified lipopeptides
INVENTOR(S): Keith, Dennis, Montclair, NJ, UNITED STATES
Lai, Jan-Ji, Westborough, MA, UNITED STATES
Govardhan, Chandrika, Lexington, MA, UNITED STATES
Khalaf, Nazer, Worcester, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2006014674	A1	20060119
APPLICATION INFO.:	US 2005-108380	A1	20050418 (11)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-23517, filed on 17 Dec 2001, ABANDONED Continuation-in-part of Ser. No. US 2001-24701, filed on 17 Dec 2001, ABANDONED Continuation-in-part of Ser. No. US 2001-24405, filed on 18 Dec 2001, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-256268P	20001218 (60)
	US 2001-274741P	20010309 (60)
	US 2001-341315P	20011213 (60)
	US 2001-340525P	20011213 (60)
	US 2000-256268P	20001218 (60)
	US 2001-274741P	20010309 (60)
	US 2001-341315P	20011213 (60)
	US 2001-340525P	20011213 (60)
	US 2000-256268P	20001218 (60)
	US 2001-274741P	20010309 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FISH & RICHARDSON PC, P.O. BOX 1022, MINNEAPOLIS, MN, 55440-1022, US
NUMBER OF CLAIMS: 132
EXEMPLARY CLAIM: 1-56
NUMBER OF DRAWINGS: 15 Drawing Page(s)
LINE COUNT: 2161
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to crystalline and crystal-like forms of lipopeptides, including daptomycin, a lipopeptide antibiotic with potent bactericidal activity against gram-positive bacteria, including strains

that are resistant to conventional antibiotics. The present invention relates to methods of purifying lipopeptides, including daptomycin, a lipopeptide antibiotic with potent bactericidal activity against gram-positive bacteria, including strains that are resistant to conventional antibiotics. The present invention also relates to pharmaceutical compositions comprising the purified form of the lipopeptide and methods of using these compositions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . of any organ or tissue in the body. These organs or tissue include, without limitation, skeletal muscle, skin, bloodstream, kidneys, **heart**, lung and bone. The method of the invention may be used to treat, without limitation, skin and soft tissue infections,. . .

DETD . . . KA 159, Dynemicin A, DX8739, DU 6681; Cefluprenam, ER 35786, Cefoselis, Sanfetrinem celexetil, HGP.sub.--31, Cefpirome, HMR.sub.--3647, RU.sub.--59863, Mersacidin, KP 736, **Rifalazil**; Kosan, AM 1732, MEN 10700, Lenapenem, BO 2502A, NE.sub.--1530, PR 39, K130, OPC 20000, OPC 2045, Veneprim, PD 138312, PD. . .

L166 ANSWER 23 OF 40 USPATFULL on STN

ACCESSION NUMBER: 2005:234067 USPATFULL

TITLE: Novel lipopeptides as antibacterial agents

INVENTOR(S): Hill, Jason, Auburndale, MA, UNITED STATES
Parr, Ian, Medford, MA, UNITED STATES
Morytko, Michael, Framingham, MA, UNITED STATES
Siedlecki, Jim, Burlington, MA, UNITED STATES
Yu, Xian Yang, Billerica, MA, UNITED STATES
Silverman, Jared, Brookline, MA, UNITED STATES
Keith, Dennis, Arlington, MA, UNITED STATES
Finn, John, Stow, MA, UNITED STATES
Christensen, Dale, Apex, NC, UNITED STATES
Lazarova, Tsvetelina, Brookline, MA, UNITED STATES
Watson, Alan D., Lexington, MA, UNITED STATES
Zhang, Yan, Sharon, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005203006	A1	20050915
APPLICATION INFO.:	US 2005-121851	A1	20050504 (11)

RELATED APPLN. INFO.: Division of Ser. No. US 2000-738742, filed on 15 Dec 2000, GRANTED, Pat. No. US 6911525

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-170943P	19991215 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: CUBIST PHARMACEUTICALS, INC., 65 HAYDEN AVENUE, LEXINGTON, MA, 02421, US

NUMBER OF CLAIMS: 29

EXEMPLARY CLAIM: 1

LINE COUNT: 2346

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel lipopeptide compounds. The invention also relates to pharmaceutical compositions of these compounds and methods of using these compounds as antibacterial compounds. The invention also relates to methods of producing these novel lipopeptide compounds and intermediates used in producing these compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . the bacterial infection is caused by gram-positive bacteria. These organs or tissue include, without limitation, skeletal muscle, skin, bloodstream, kidneys, **heart**, lung and bone. The method of the invention may be used to treat, without limitation, skin and soft tissue infections,. . .

DETD . . . KA 159, Dynemicin A, DX8739, DU 6681; Cefluprenam, ER 35786, Cefoselis, Sanfetrinem celexetil, HGP-31, Cefpirome, HMR-3647, RU-59863, Mersacidin, KP 736, **Rifalazil**; Kosan, AM 1732, MEN 10700, Lenapenem, BO 2502A, NE-1530, PR 39, K130, OPC 20000, OPC 2045, Veneprim, PD 138312, PD. . .

CLM What is claimed is:

. . . acid 1-[(cyclohexyloxy)carbonyl]oxy]ethyl ester), cefpirome (1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-6,7-dihydro-5H-cyclopenta[b]pyridinium inner salt), HMR-3647 (3-de[(2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl)oxy]-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl[[4-[4-(3-pyridinyl)-1H-imidazol-1-yl]butyl]imino]]-erythromycin), RU-59863 (C-7 catechol substituted cephalosporin), KP 736 ((6R,7R)-7-[[(2Z)-(2-amino-4-thiazolyl)[[(1,4-dihydro-1,5-dihydroxy-4-oxo-2-pyridinyl)methoxy]imino]acetyl]amino]-8-oxo-3-[(1,2,3-thiadiazol-5-ylthio)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid disodium salt), **Rifalazil** (1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo-rifamycin VIII), MEN 10700 ((5R,6S)-3-[[(2-amino-2-oxoethyl)methylamino]methyl]-6-[(1R)-1-hydroxyethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid), lenapenem ((4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-3-[[(3S,5S)-5-[(1R)-1hydroxy-3-(methylamino)propyl]-3-pyrrolidinyl]thio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid), BO 2502A ((4R,5S,6S)-3-[(2S,3'S,4S)-[2,3'-bipyrrolidin]-4-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid), NE-1530 (3'-sialyllacto-N-neotetraose), K130 (5-[[4-[3-[[4-[(4-aminophenyl)sulfonyl]phenyl]amino]propoxy]-3,5-dimethoxyphenyl]methyl]-2,4-pyrimidinediamine), PD 138312 ((R)-7-[3-(1-amino-1-methylethyl)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic. . .

IT 54-85-3, Isoniazid 56-75-7, Chloramphenicol 58-14-0, Pyrimethamine 61-32-5, Methicillin 61-33-6, biological studies 65-49-6, Paraaminosalicylic acid 68-41-7, Cycloserine 74-55-5, Ethambutol 98-96-4, Pyrazinamide 104-06-3, Thiacetazone 154-21-2, Lincomycin 303-81-1, Novobiocin 443-48-1, Metronidazole 536-33-4, Ethionamide 587-23-5, Methenamine mandelate 738-70-5, Trimethoprim 751-94-0, Fusidate sodium 1403-66-3, Gentamicin 1404-90-6, Vancomycin 1405-87-4, Bacitracin 1405-97-6, Gramicidin 1695-77-8, Spectinomycin 5714-73-8, Methenamine hippurate 11003-38-6, Capreomycin 12650-69-0, Mupirocin 14222-60-7, Prothionamide 15318-45-3, Thiamphenicol 18323-44-9, Clindamycin 23155-02-4, Fosfomycin 32988-50-4, Viomycin 37517-28-5, Amikacin 56391-56-1, Netilmicin 61036-62-2, Teicoplanin 64221-86-9, Imipenem 65243-33-6 73090-70-7, Epiroprim 73384-59-5, Ceftriaxone 78110-38-0, Aztreonam 84957-29-9, Cefpirome 87638-04-8, Carumonam 99376-22-4, Ritipenem acoxyl 109545-84-8, Ziracin 111452-88-1 113359-04-9, Cefozopran 116853-25-9, Cefluprenam 120410-24-4, Biapenem 120788-07-0, Sulopenem 122841-10-5, Cefoselis 124412-57-3, Dynemicin A 126602-89-9, Synercid 128104-18-7, Mersacidin **129791-92-0**, Rifalazil 129951-17-3, DU 6681 133686-28-9, KP 736 138126-04-2, BO 2502A 139637-11-9, PR 39 141611-76-9, Sanfetrinem sodium 141646-08-4, Sanfetrinem-cilexetil 143158-16-1, PD 138312 143383-20-4 145260-69-1, CP 111905 147214-63-9, Cyclothialidine 149137-72-4 149951-16-6, Lenapenem

157542-49-9, CS-834 158295-97-7, TOC 39 161856-02-6, OCA-983
165800-03-3, Linezolid 171099-57-3, LY333328 176950-36-0, Micacocidin
A 186319-97-1, ER 35786 191114-48-4, HMR3647 194804-75-6, T 3811
195874-55-6, MEN 10700 205925-96-8, Sch 40832 224452-66-8, SB 275833
252188-71-9, Ro 65-5788 345631-66-5, Eveminomycin 345631-69-8, CL
331022 345631-70-1, KA 159 345631-86-9, GV 143253 345631-92-7, A
99058.1 345631-93-8, A 165600 345631-94-9, A 179796 345631-96-1,
HGP 31 345631-97-2, RU 59863 345631-98-3, Kosan 345631-99-4, AM
1732 345632-00-0, NE 1530 345632-01-1, OPC 20000 345632-02-2, OPC
2045 345632-44-2, Veneprim 345632-48-6, SEP 132613 345632-68-0
345632-69-1, SUN-A 0026
(preparation of novel lipopeptides as antibacterial agents)

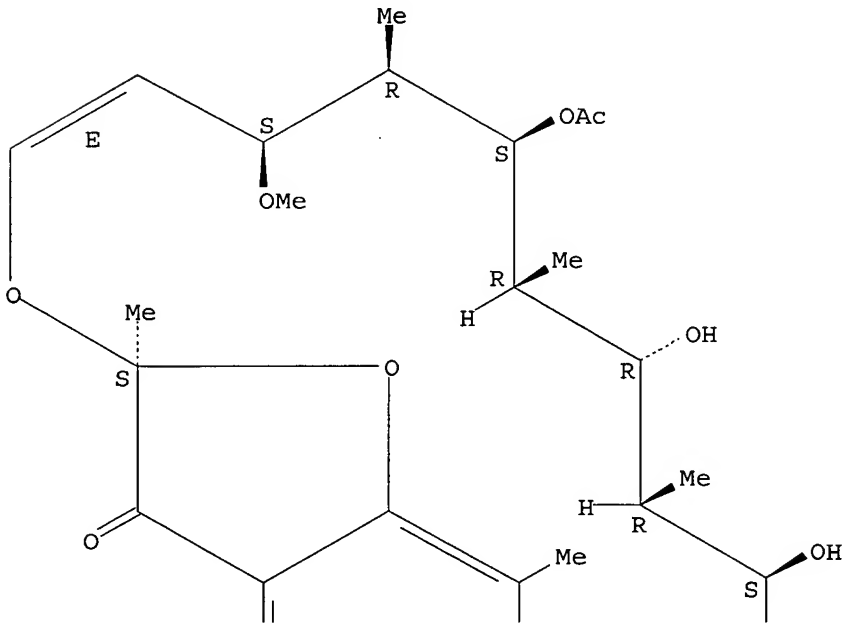
IT **129791-92-0**, Rifalazil
(preparation of novel lipopeptides as antibacterial agents)

RN 129791-92-0 USPATFULL

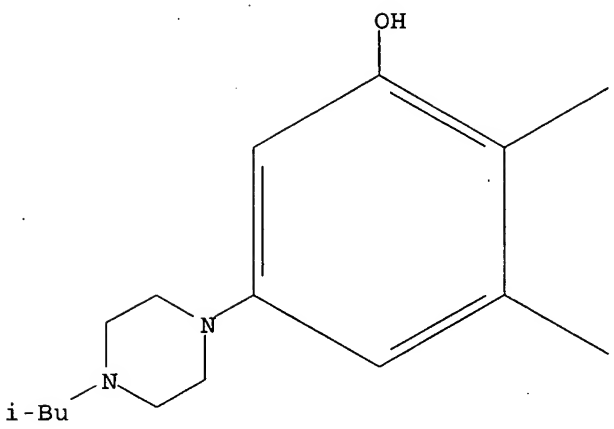
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

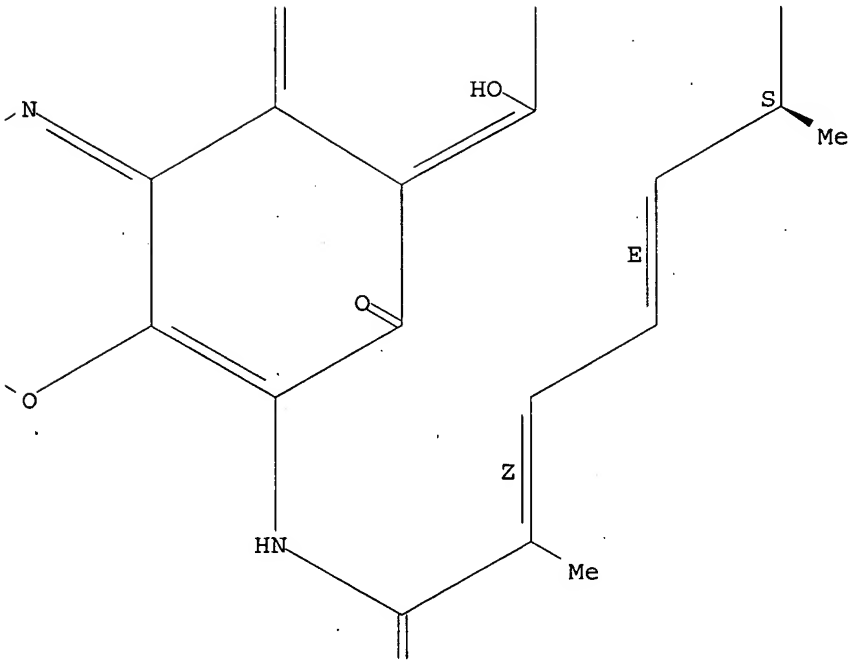
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

O

L166 ANSWER 24 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2005:31675 USPATFULL
TITLE: Compositions and methods relating to the daptomycin biosynthetic gene cluster

INVENTOR(S): Miao, Vivian Pak Woon, Surrey, CANADA
Brian, Paul, Waltham, MA, UNITED STATES
Baltz, Richard H., Lincoln, MA, UNITED STATES
Coeffet-LeGal, Marie Francoise, Arlington, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005027113	A1	20050203
APPLICATION INFO.:	US 2002-211028	A1	20020731 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. WO 2001-US32354, filed on 17 Oct 2001, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-379866P	20020510 (60)
	US 2001-310385P	20010806 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: CUBIST PHARMACEUTICALS, INC., 65 HAYDEN AVENUE, LEXINGTON, MA, 02421
NUMBER OF CLAIMS: 73
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 19 Drawing Page(s)
LINE COUNT: 6301
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides nucleic acid molecules comprising all or a part of a daptomycin biosynthetic gene cluster. The daptomycin biosynthetic gene cluster may be derived from Streptomyces, preferably from S. roseosporus. The invention also provides other nucleic acid molecules from S. roseosporus. The invention further provides polypeptides encoded by the nucleic acid molecules, antibodies that specifically bind to the polypeptides, and methods of using the nucleic acid molecules, polypeptides and antibodies to produce daptomycin and other compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . of any organ or tissue in the body. These organs or tissue include, without limitation, skeletal muscle, skin, bloodstream, kidneys, **heart**, lung and bone. The method of the invention may be used to treat, without limitation, skin and soft tissue infections,. . .

DETD . . . KA 159, Dynemicin A, DX8739, DU 6681; Cefluprenam, ER 35786, Cefoselis, Sanfetrinem celexetil, HGP-31, Cefpirome, HMR-3647, RU-59863, Mersacidin, KP 736, **Rifalazil**; Kosan, AM 1732, MEN 10700, Lenapenem, BO 2502A, NE-1530, PR 39, K130, OPC 20000, OPC 2045, Veneprim, PD 138312, PD. . .

L166 ANSWER 25 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2005:11612 USPATFULL
TITLE: High purity lipopeptides
INVENTOR(S): Kelleher, Thomas, Weston, MA, UNITED STATES
Lai, Jan-Ji, Westborough, MA, UNITED STATES
DeCourcey, Joseph P., Charlestown, MA, UNITED STATES
Lynch, Paul, Arlington, MA, UNITED STATES
Zenoni, Maurizio, Milan, ITALY
Tagliani, Auro, Pavia, ITALY

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005009747	A1	20050113

APPLICATION INFO.: US 2003-747485 A1 20031229 (10)
RELATED APPLN. INFO.: Division of Ser. No. US 2000-735191, filed on 28 Nov 2000, GRANTED, Pat. No. US 6696412

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-177170P	20000120 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: CUBIST PHARMACEUTICALS, INC., 65 HAYDEN AVENUE, LEXINGTON, MA, 02421
NUMBER OF CLAIMS: 29
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 11 Drawing Page(s)
LINE COUNT: 2313
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention discloses highly purified daptomycin and to pharmaceutical compositions comprising this compound. The invention discloses a method of purifying daptomycin comprising the sequential steps of anion exchange chromatography, hydrophobic interaction chromatography and anion exchange chromatography. The invention also discloses a method of purifying daptomycin by modified buffer enhanced anion exchange chromatography. The invention also discloses an improved method for producing daptomycin by fermentation of Streptomyces roseosporus. The invention also discloses high pressure liquid chromatography methods for analysis of daptomycin purity. The invention also discloses lipopeptide micelles and methods of making the micelles. The invention also discloses methods of using lipopeptide micelles for purifying lipopeptide antibiotics, such as daptomycin. The invention also discloses using lipopeptide micelles therapeutically.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . of any organ or tissue in the body. These organs or tissue include, without limitation, skeletal muscle, skin, bloodstream, kidneys, **heart**, lung and bone. The method of the invention may be used to treat, without limitation, skin and soft tissue infections, . . .

DETD . . . KA 159, Dynemicin A, DX8739, DU 6681; Cefluprenam, ER 35786, Cefoselis, Sanfetrinem celexetil, HGP-31, Cefpirome, HMR-3647, RU-59863, Mersacidin, KP 736, **Rifalazil**; Kosan, AM 1732, MEN 10700, Lenapenem, BO 2502A, NE-1530, PR 39, K130, OPC 20000, OPC 2045, Veneprim, PD 138312, PD. . .

IT 54-85-3, Isoniazid 56-75-7, Chloramphenicol 58-14-0, Pyrimethamine 60-54-8, Tetracycline 65-49-6, Paraaminosalicylic acid 68-41-7, Cycloserine 74-55-5, Ethambutol 98-96-4, Pyrazinamide 104-06-3, Thiacetazone 154-21-2, Lincomycin 303-81-1, Novobiocin 443-48-1, Metronidazole 536-33-4, Ethionamide 738-70-5, Trimethoprim 751-94-0, Fusidate sodium 1400-61-9, Nystatin 1403-66-3, Gentamicin 1404-90-6, Vancomycin 1405-87-4, Bacitracin 1405-97-6, Gramicidin 1406-05-9, Penicillin 1406-11-7, Polymyxin 1695-77-8, Spectinomycin 2022-85-7, Flucytosine 5714-73-8, Methenamine hippurate 6998-60-3, Rifamycin 7681-93-8, Pimaricin 11003-38-6, Capreomycin 11006-76-1, Streptogramin 11076-17-8, Sordarin 11111-12-9, Cephalosporin 12633-72-6, Amphotericin 12650-69-0, Mupirocin 14222-60-7, Prothionamide 15318-45-3, Thiamphenicol 18323-44-9, Clindamycin 23155-02-4, Fosfomycin 32988-50-4, Viomycin 37517-28-5, Amikacin 51667-26-6, Oxazolidinone 56391-56-1, Netilmicin 61036-62-2, Teicoplanin 64221-86-9, Imipenem 65243-33-6 65277-42-1, Ketoconazole 65472-88-0, Naftifine 73090-70-7, Epiroprim 73384-59-5, Ceftriaxone 78110-38-0, Aztreonam 82800-75-7, Antibiotic

A 21978 83200-96-8, Carbapenem 84625-61-6, Itraconazole 84957-29-9, Cefpirome 86386-73-4, Fluconazole 87638-04-8, Carumonam 91161-71-6, Terbinafine 99376-22-4 109545-84-8, Ziracin 111452-88-1, K130 113359-04-9, Cefozopran 116853-25-9, Cefluprenam 120410-24-4, Biapenem 120788-07-0, Sulopenem 122672-46-2, Cispentacin 122841-10-5, Cefoselis 124412-57-3, Dynemicin A 126602-89-9, Synercid 128104-18-7, Mersacidin **129791-92-0**, Rifalazil 129951-17-3, DU 6681 133686-28-9, KP 736 138126-04-2, BO 2502A 139637-11-9, PR 39 141611-76-9, Sanfetrinem sodium 141646-08-4, Sanfetrinem cilexetil 143158-16-1, PD 138312 143383-20-4, PD 140248 145078-62-2, MerWF3010 145260-69-1, CP 111905 147214-63-9, Cyclothialidine 149137-72-4, DX8739 149951-16-6, Lenapenem 154445-06-4, CL 331002 157542-49-9, CS-834 157998-96-4, Azoxybacilin 158295-97-7, TOC 39 161856-02-6, OCA-983 171099-57-3, LY 333328 176950-36-0, Micacocidin A 180462-26-4, Arthrichitin 180992-28-3, Khafrefungin 185377-91-7, LL 15G256γ 186319-97-1, ER 35786 188793-60-4, Antibiotic A 54145 191114-48-4, HMR 3647 194804-75-6, T 3811 195874-55-6, MEN 10700 199169-60-3, Corynecandin 205925-96-8, Sch 40832 224452-66-8, SB-275833 252188-71-9, Ro 65-5788 345631-66-5, Eveminomycin 345631-70-1, KA 159 345631-86-9, GV-143253 345631-92-7, A-99058.1 345631-93-8, A-165600 345631-94-9, A-179796 345631-96-1, HGP-31 345631-97-2, RU-59863 345631-98-3, Kosan 345631-99-4, AM 1732 345632-00-0, NE-153O 345632-01-1, OPC 20000 345632-02-2, OPC 2045 345632-44-2, Veneprim 345632-48-6, SEP-132613 345632-68-0, SR-15402 345632-69-1, SUN A0026 351496-61-2, LY 33328 351496-93-0, HMR 364
(purification of lipopeptides and lipopeptide micelles)

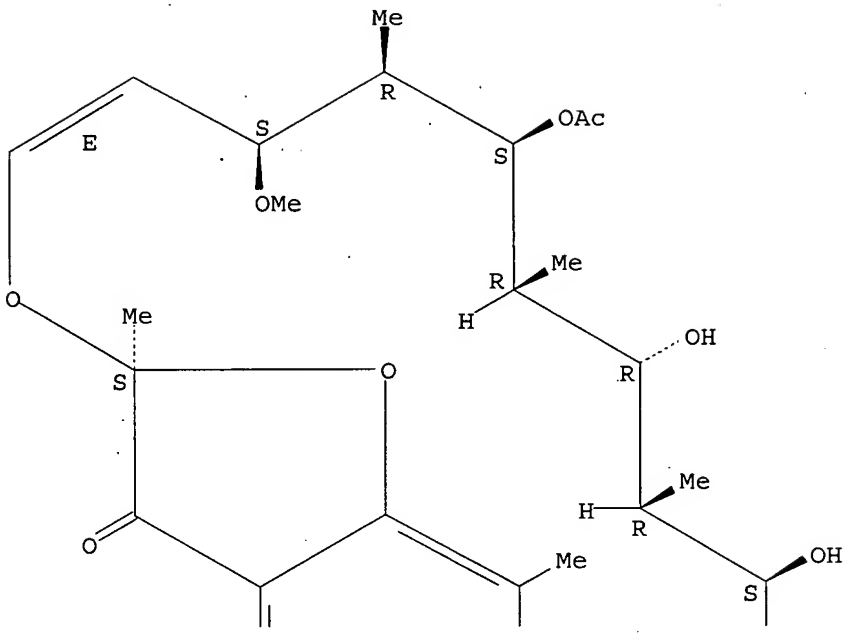
IT **129791-92-0**, Rifalazil
(purification of lipopeptides and lipopeptide micelles)

RN 129791-92-0 USPATFULL

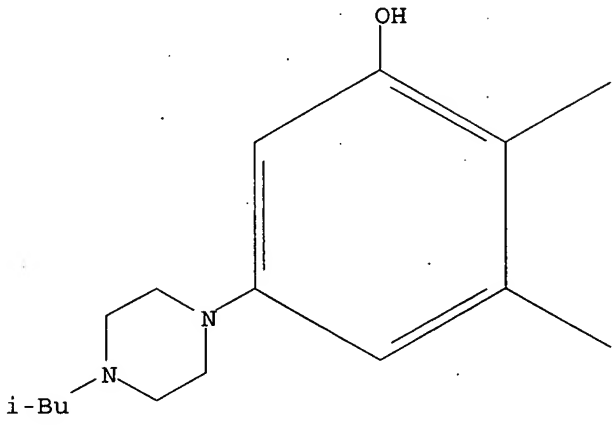
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

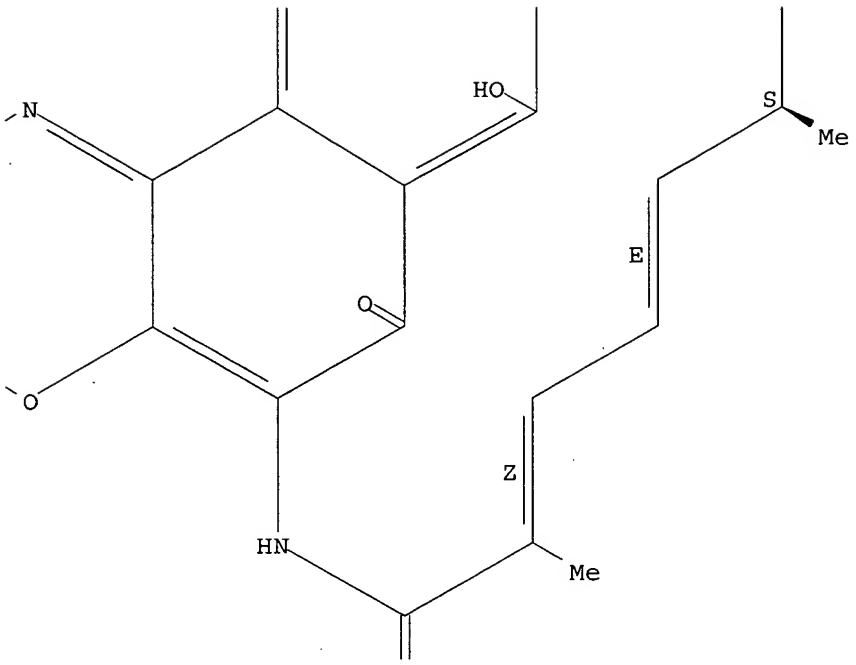
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

O

L166 ANSWER 26 OF 40 USPATFULL on STN

ACCESSION NUMBER:	2004:334894 USPATFULL
TITLE:	Methods and compositions for immunomodulation using CD1 antigens
INVENTOR(S):	Moody, D. Branch, West Roxbury, MA, UNITED STATES Young, David C., Benton, ME, UNITED STATES Costello, Catherine E., Reading, MA, UNITED STATES
PATENT ASSIGNEE(S):	The Brigham and Women's Hospital, Inc., Boston, MA, UNITED STATES (U.S. corporation) Trustees of Boston University, Boston, MA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004265976	A1	20041230	
APPLICATION INFO.:	US 2004-827616	A1	20040419	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-464228P	20030418 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	Maria A. Trevisan, 600 Atlantic Avenue, Boston, MA, 02210
NUMBER OF CLAIMS:	45

EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 9 Drawing Page(s)
LINE COUNT: 2030
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to novel CD1a-presented antigens. These antigens can be used as antigens, adjuvants or as immunomodulatory agents in a variety of diagnostic, therapeutic and prophylactic applications.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . Listeria monocytogenes, Mycobacteria spp. (e.g., M. tuberculosis, M. avium, M. gordonae, M. intracellulare, and M. kansasii), Neisseria gonorrhoeae, Neisseria meningitidis, **Nocardia** asteroides, **Nocardia** brasiliensis, Pasturella multocida, Peptostreptococcus spp., Proteus spp., Pseudomonas aeruginosa, other Pseudomonas spp., Rickettsia, Salmonella spp., Serratia spp., Shigella spp., Staphylococcus. . .
DETD . . . abscess; etc. The invention also is useful with non-intraabdominal surgeries such as orthopedic surgeries, pelvic and gynecologic surgeries, urologic surgeries, **cardiothoracic** surgeries, neurosurgeries, plastic and reconstructive surgeries, vascular surgeries, head and neck surgeries, and surgeries to correct wound infections. These listed. . .
DETD . . . plasmid DNA in biodegradable microparticles, azoles known to be inhibitors of cytochromes P450, 3-aryl-2-(1H-benzotriazol-1-yl)acrylonitriles, thiolactomycin analogues, sparfloxacin, benzoxazinorifamycins such as **KRM-1648**, rifampicin, phenothiazines, pyrazinamide, pro-drug ethionamide, and the like.

L166 ANSWER 27 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2004:88902 USPATFULL
TITLE: Novel lipopeptides as antibacterial agents
INVENTOR(S): Hill, Jason, Auburndale, MA, UNITED STATES
Parr, Ian, Medford, MA, UNITED STATES
Morytko, Michael, Framingham, MA, UNITED STATES
Siedlecki, Jim, Burlington, MA, UNITED STATES
Yang Yu, Xiang, Billerica, MA, UNITED STATES
Silverman, Jared, Brookline, MA, UNITED STATES
Keith, Dennis, Arlington, MA, UNITED STATES
Finn, John, Stow, MA, UNITED STATES
Christensen, Dale, Apex, NC, UNITED STATES
Lazarova, Tsvetelina, Brookline, MA, UNITED STATES
Watson, Alan D., Lexington, MA, UNITED STATES
Zhang, Yan, Sharon, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004067878	A1	20040408
APPLICATION INFO.:	US 2000-737908	A1	20001215 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-170946P	19991215 (60)
	US 2000-208222P	20000530 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: CUBIST PHARMACEUTICALS, INC., 65 HAYDEN AVENUE, LEXINGTON, MA, 02421
NUMBER OF CLAIMS: 31
EXEMPLARY CLAIM: 1
LINE COUNT: 5994

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel lipopeptide compounds. The invention also relates to pharmaceutical compositions of these compounds and methods of using these compounds as antibacterial compounds. The invention also relates to methods of producing these novel lipopeptide compounds and intermediates used in producing these compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . the bacterial infection is caused by gram-positive bacteria. These organs or tissue include, without limitation, skeletal muscle, skin, bloodstream, kidneys, **heart**, lung and bone. The method of the invention may be used to treat, without limitation, skin and soft tissue infections,. . .

SUMM . . . KA 159, Dynemicin A, DX8739, DU 6681; Cefluprenam, ER 35786, Cefoselis, Sanfetrinem celexetil, HGP-31, Cefpirome, HMR-3647, RU-59863, Mersacidin, KP 736, **Rifalazil**; Kosan, AM 1732, MEN 10700, Lenapenem, BO 2502A, NE-1530, PR 39, K130, OPC 20000, OPC 2045, Veneprim, PD 138312, PD. . .

CLM What is claimed is:

. . . KA 159, Dynemicin A, DX8739, DU 6681; Cefluprenam, ER 35786, Cefoselis, Sanfetrinem celexetil, HGP-31, Cefpirome, HMR-3647, RU-59863, Mersacidin, KP 736, **Rifalazil**; Kosan, AM 1732, MEN 10700, Lenapenem, BO 2502A, NE-1530, PR 39, K130, OPC 20000, OPC 2045, Veneprim, PD 138312, PD. . .

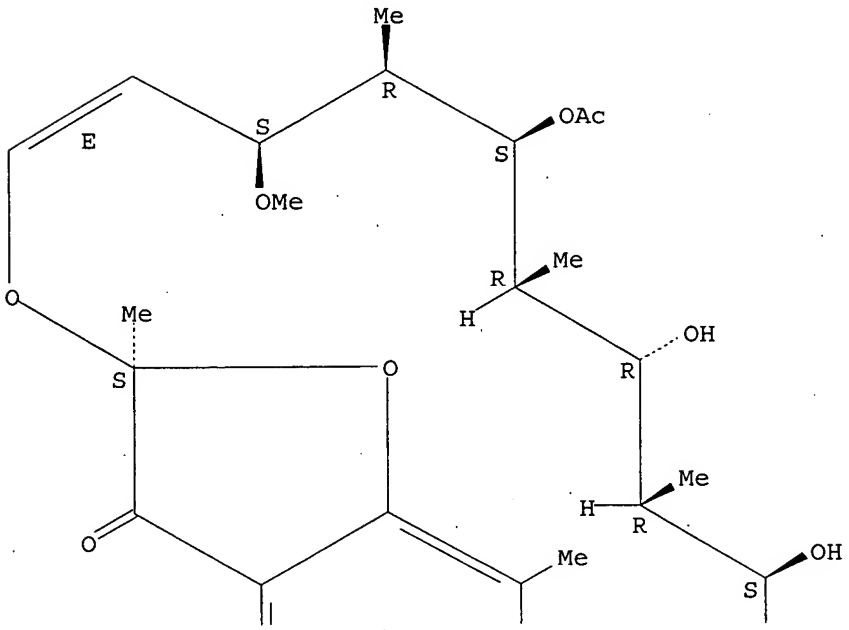
IT 54-85-3, Isoniazid 56-75-7, Chloramphenicol 58-14-0, Pyrimethamine 61-32-5, Methicillin 61-33-6, biological studies 65-49-6, Paraaminosalicylic acid 68-41-7, Cycloserine 74-55-5, Ethambutol 98-96-4, Pyrazinamide 104-06-3, Thiacetazone 154-21-2, Lincomycin 303-81-1, Novobiocin 443-48-1, Metronidazole 536-33-4, Ethionamide 587-23-5, Methenamine mandelate 738-70-5, Trimethoprim 751-94-0, Fusidate sodium 1403-66-3, Gentamicin 1404-90-6, Vancomycin 1405-87-4, Bacitracin 1405-97-6, Gramicidin 1695-77-8, Spectinomycin 5714-73-8, Methenamine hippurate 11003-38-6, Capreomycin 12650-69-0, Mupirocin 14222-60-7, Prothionamide 15318-45-3, Thiamphenicol 18323-44-9, Clindamycin 23155-02-4, Fosfomycin 32988-50-4, Viomycin 37517-28-5, Amikacin 56391-56-1, Netilmicin 61036-62-2, Teicoplanin 64221-86-9, Imipenem 65243-33-6 73090-70-7, Epiroprim 73384-59-5, Ceftriaxone 78110-38-0, Aztreonam 84957-29-9, Cefpirome 87238-52-6 87638-04-8, Carumonam 109545-84-8, Ziracin 111452-88-1 113359-04-9, Cefozopran 116853-25-9, Cefluprenam 120410-24-4, Biapenem 120788-07-0, Sulopenem 122841-10-5, Cefoselis 124412-57-3, Dynemicin A 126602-89-9, Synercid 128104-18-7, Mersacidin **129791-92-0**, Rifalazil 129951-17-3, DU 6681 133686-28-9, KP 736 138126-04-2, BO 2502A 139637-11-9, PR 39 141611-76-9, Sanfetrinem sodium 141646-08-4, Sanfetrinem-cilexetil 143158-16-1, PD 138312 143383-20-4 145260-69-1, CP 111905 147214-63-9, Cyclothialidine 149137-72-4 149951-16-6, Lenapenem 157542-49-9, CS-834 158295-97-7 161856-02-6, OCA-983 165800-03-3, Linezolid 171099-57-3, LY333328 176950-36-0, Micacocidin A 186319-97-1, ER 35786 191114-48-4, HMR3647 194804-75-6, T 3811 195874-55-6, MEN 10700 205925-96-8 224452-66-8, SB 275833 252188-71-9 345631-66-5, Eveminomycin 345631-69-8, CL 331022 345631-70-1, KA 159 345631-86-9, GV 143253 345631-92-7, A 99058.1 345631-93-8, A 165600 345631-94-9, A 179796 345631-96-1, HGP 31 345631-97-2, RU 59863 345631-98-3, Kosan 345631-99-4, AM 1732 345632-00-0, NE 1530 345632-01-1, OPC 20000 345632-02-2, OPC 2045 345632-44-2, Veneprim 345632-48-6, SEP 132613 345632-68-0, SR 15402 345632-69-1, SUN-A 0026
(preparation of lipopeptides as antibacterial agents)

IT **129791-92-0**, Rifalazil
(preparation of lipopeptides as antibacterial agents)

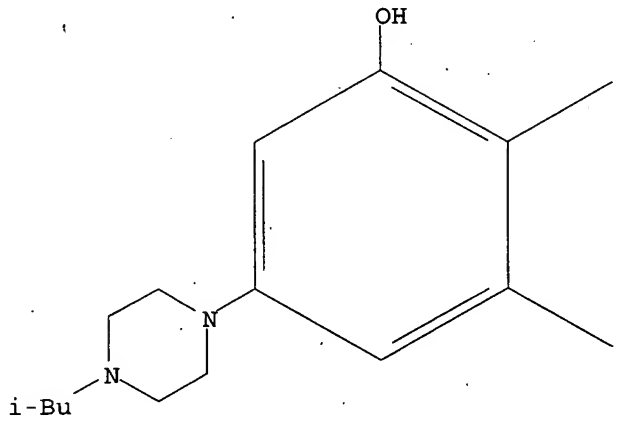
RN 129791-92-0 USPATFULL
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

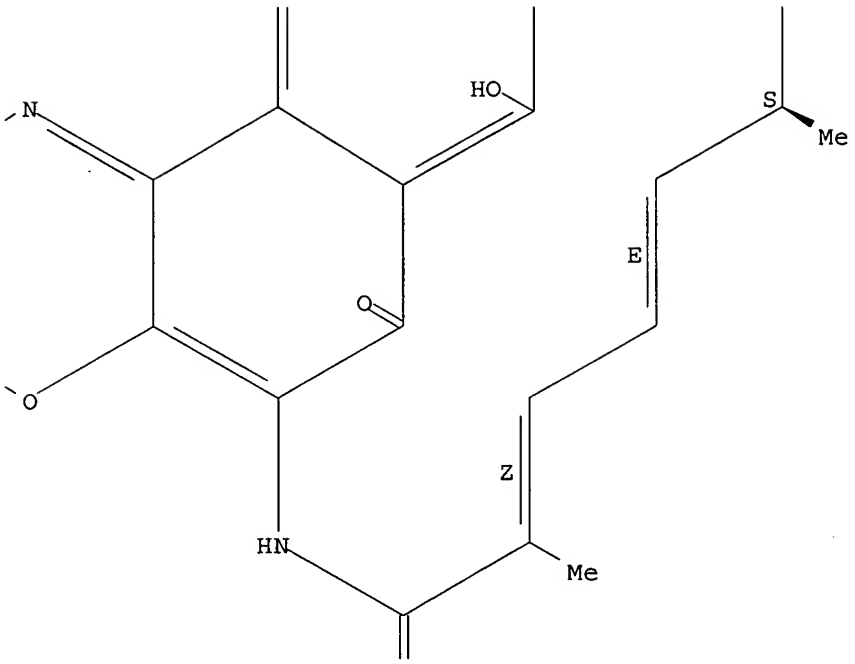
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

O

L166 ANSWER 28 OF 40 USPATFULL on STN

ACCESSION NUMBER:	2004:38715 USPATFULL
TITLE:	Method of screening anti-bacterial agents for effectiveness in treating persistant intracellular infections
INVENTOR(S):	Stamm, Walter E., Seattle, WA, UNITED STATES Suchland, Robert J., Seattle, WA, UNITED STATES
PATENT ASSIGNEE(S):	University of Washington (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004029254	A1	20040212	
APPLICATION INFO.:	US 2003-438287	A1	20030513	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-380896P	20020515 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	CHRISTENSEN, O'CONNOR, JOHNSON, KINDNESS, PLLC, 1420 FIFTH AVENUE, SUITE 2800, SEATTLE, WA, 98101-2347
NUMBER OF CLAIMS:	14
EXEMPLARY CLAIM:	1
LINE COUNT:	768

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present application provides methods of screening anti-bacterial agents for effectiveness in treating persistent intracellular infection by bacteria capable of forming intracytoplasmic inclusions in cells.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . is also transmitted from person-to-person and is the causative agent of a typical pneumonia (walking pneumonia), pharyngitis, bronchitis, sinusitis, and **atherosclerosis.** C. psittaci is typically transmitted through contact with an infected bird or bird droppings and is the causative agent of. . .

DETD [0056] MIC and MCC determinations for seven different anti-bacterial agents (doxycycline, azithromycin, ofloxacin, tetracycline, erythromycin, rifampin, and **rifalazil** (**KRM-1648**)) were compared in order to determine the relative efficacy of each agent in treating a persistent Chlamydia infection. Table 5 summarizes the MIC and MCC determinations for the seven anti-bacterial agents. The MCC for all drugs except **rifalazil** was many fold higher than the MIC, indicating chlamydial survival in concentrations of anti-bacterial well beyond the MIC for most. . . small number of organisms at high concentrations of drug. These results are consistent with heterotypic survival. Compared with other drugs, **rifalazil** , an experimental anti-chlamydial compound, was highly active and appeared bactericidal at concentrations much closer to the MIC level. For all of the compounds except **rifalazil**, the MCC.sub.3/MIC ratio was greater than 128. These results demonstrate the variation in efficacy of anti-bacterial agents in the treatment. . . 1000

Azithromycin	0.125	8	64	512
Ofloxacin	1.0	16	128	128
Tetracycline	0.25	16	128	128
Erythromycin	0.5	8	128	256
Rifampin	0.016	0.5	4	250
Rifalazil	0.00025	0.002	0.004	16

.sup.AInhibitory concentrations given in μg/ml.

DETD [0057] MIC and MCC determinations for five different anti-bacterials (**rifalazil**, KRM-1657, doxycycline, azithromycin, ofloxacin) were compared in order to determine the relative efficacy of each microbial in treating a persistent. . . and MCC determinations for the five anti-bacterial agents using clinical isolates of C. trachomatis. The MCC.sub.3 for all drugs except **rifalazil** and KRM-1657 was many fold higher than the MIC indicating chlamydial survival in concentrations of anti-bacterial well beyond the MIC for most drugs. **Rifalazil** and KRM-1657 are experimental anti-chlamydial compounds, which were highly active and appeared bactericidal at concentrations much closer to the MIC. . .

DETD . . . eradicating acute infections versus those effective at eradicating chronic infections, allows clinicians to select the appropriate anti-bacterial agent, such as **rifalazil** in the case of these particular clinical isolates, for treatment.

TABLE 6

IN VITRO DRUG SUSCEPTIBILITIES ON CLINICAL ISOLATES OF C. TRACHOMATIS.sup.A

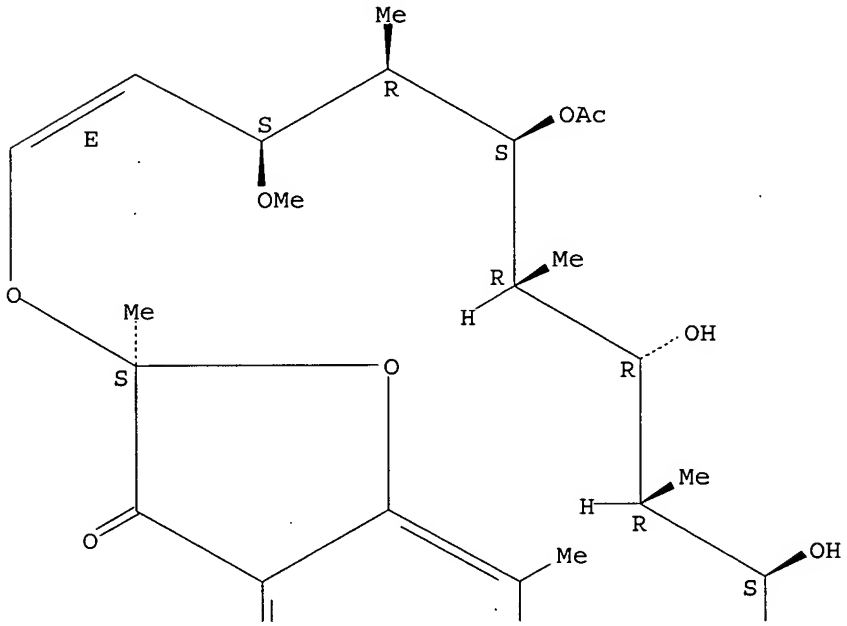
Drug	MIC	MCC.sub.1	MCC.sub.3	MCC.sub.3/MIC
Rifalazil	0.00025-0.005	0.001-0.002	0.004-0.008	16
KRM-1657	0.000064-0.000125	0.0005-0.001	0.001-0.002	16

Doxycycline	0.064-0.125	4-8	32-64	1000
Azithromycin	0.125-0.250	4-8	32-64	512
Ofloxacin	1.0-2.0	8-16	>128	128

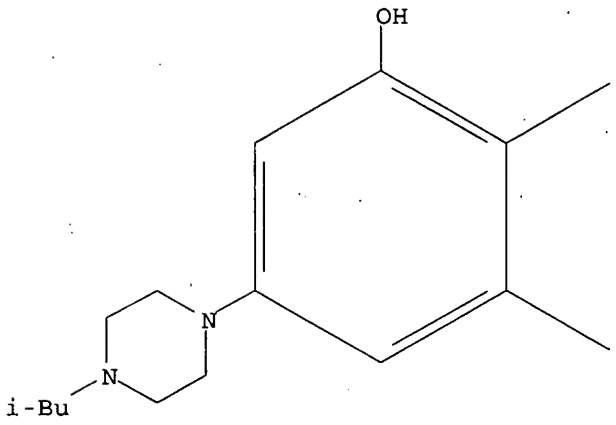
.sup.AAll. . .
IT 60-54-8, Tetracycline 114-07-8, Erythromycin 564-25-0, Doxycycline
13292-46-1, Rifampin 82419-36-1, Ofloxacin 83905-01-5, Azithromycin
129791-92-0, Rifalazil 133633-12-2, KRM-1657
(method of screening antibacterial agents for effectiveness in treating persistent intracellular infections)
IT **129791-92-0**, Rifalazil
(method of screening antibacterial agents for effectiveness in treating persistent intracellular infections)
RN 129791-92-0 USPATFULL
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

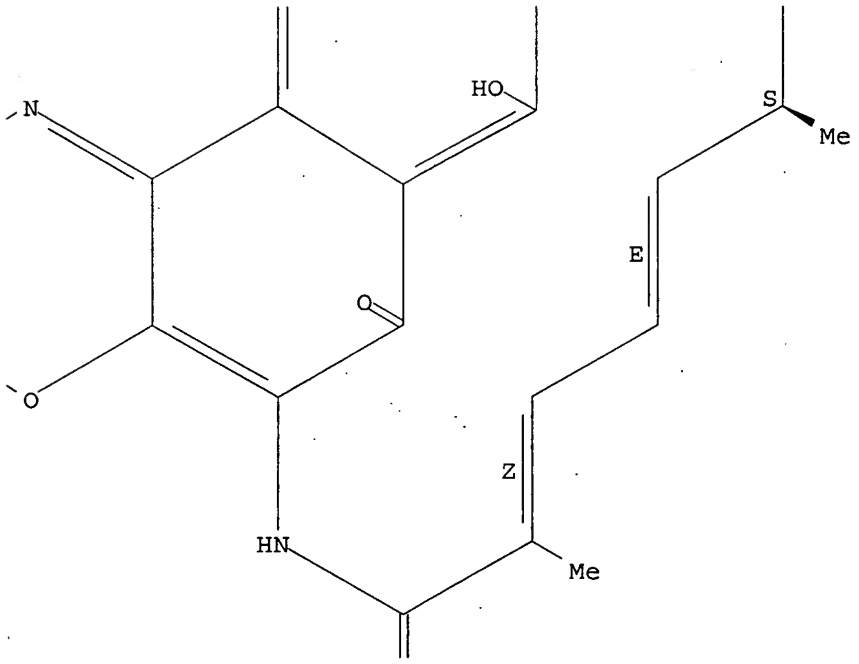
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

O

L166 ANSWER 29 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2004:31152 USPATFULL
TITLE: Novel therapeutic agents that modulate enzymatic processes

INVENTOR(S): Griffin, John H., Atherton, CA, UNITED STATES
Judice, J. Kevin, El Granada, CA, UNITED STATES
Christensen, Burton G., Alamo, CA, UNITED STATES
Jenkins, Thomas E., La Honda, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004023290	A1	20040205
APPLICATION INFO.:	US 2002-161279	A1	20020603 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-502938, filed on 11 Feb 2000, PENDING Continuation of Ser. No. US 1999-328071, filed on 8 Jun 1999, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-88448P	19980608 (60)
	US 1998-93072P	19980716 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: THERAVANCE, INC., 901 GATEWAY BOULEVARD, SOUTH SAN FRANCISCO, CA, 94080
NUMBER OF CLAIMS: 33
EXEMPLARY CLAIM: 1
LINE COUNT: 5694
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Novel multi-binding compounds are disclosed that modulate enzymatic processes. The compounds of the invention comprise from 2-10 ligands covalently connected, each of said ligands being capable of binding to an enzyme, enzyme substrate or enzyme cofactor thereby modulating the biological processes/functions thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . epalrestat, WF-2421, BAL AR-18
Diabetic nephropathy
HMG-CoA reductase Hypercholesteremia
Mevastatin, lovastatin, simvastatin, pravastatin, fluvastatin,
(1.1.1.34) Hyperlipidemia
atorvastatin, cerivastatin, dalvastatin, nisvastatin, BB-476, L-
Atherosclerosis
659699, glenvastatin, CP-83101, BMS-180431, SR-12813, DMP-
565,
L-669262, carvastatin, S-2467, S-2468, PD-135022, SQ-
33600,
crilvastatin, rawsonol, bervastatin, S-4522, acitemate, U-
. . . Hypotension L-NMMA, HMN-1180, A-84643,
3936W92, 546C88, HF-2035,
(1.14.13.39) Septic shock SC-59039,
CHU-148, AR-R-17477, BN-80933, 7-nitroindazole,
Inflammation ARL-16566
Vascular disease
Rheumatoid arthritis
Cerebrovascular ischemia
Head trauma
Neuropathy
Carcinoma
Neurodegenerative disease
Sterol 14-alpba demethylase Fungal infection
Ketoconazole, fluconazole, itraconazole, clotriamzole, miconazole,
(1.14.14.1) Parasitic infection UR-9825,
UR-9746, UR-9751, Sch-56592, T-8581, Sch-42538,

Atherosclerosis
Sch-42427, GR-99060, Sch-45012, UR-9728, Sch-51048, UR-
Hypercholesterolemia 9717,
ZD-0870, voriconazole, BMS-207147, Sch-50002,
Hyperlipidemia
becliconazole, A-39806, azalanstat, etanidazole
Neoplasm
Cyclooxygenase 1 Inflammation. . . mefanmic acid, CI-1004,
P-10294, P-8977, pamicogrel,
Pruritis WY-28342,
nitroflurbiprofen, NCX-4016, lornoxicam, ML-3000,
Thromboembolism tenidap,
CS-670, FS-205-397, eltenac, CI-986, N-14, SKF-86002,
Cerebrovascular ischemia
SKF-105809, RP-66364, pirazolac, P-8892, ER-34122, tepoxalin,
Artery disease
flobufen, HN-3392, CBS-113-A, BF-389, SC-57949, PD-145246,
Rheumatoid arthritis E-5110,
FR-122047, tenoxicam, LCB-1892, PD-136005,
Pain
dexibuprofen, BW-755-C, HCT-2035, FR-140423, nabumetone,
. . . PGV-20229, NCX-4016, celecoxib, lornoxicam,
Pruritis SC-57666,
ML-3000, tenidap, CS-670, SC-58451, L-768277, L-
Thromboembolism 783003,
GR-253035, FS-205-397, eltenac, CI-986, FR-123826, N-
Cerebrovascular ischemia
14, PD-164387, SKF-86002, SKF-105809, RP-66364, pirazolac,
Artery disease
P8892, nimesulide, rofecoxib, L-761066, ER-34122, L-791456,
Rheumatoid arthritis
PD-138387, tepoxalin, flobufen, HN-3392, CBS-113-A, BF-389,
Osteoarthritis SC-57949,
PD-145246, NS-398, E-5110,. . . PD-098120-0003, L-752860, HX-0836,
diclofenac, SC-58236
Multiple sclerosis
Musculoskeletal disease
Platelet aggregation
Squalene monooxygenase Fungal infection
Terbinafine, naftifine, NB-598, FR-194738, SDZ-87-469, Ro-44-
(1.14.99.7) **Atherosclerosis**
2104, FW- 1045, SDZ-880-540
Hypercholesterolemia
Hyperlipidemia
Coronary **artery** disease
Steroid 17-alpha hydroxylase Prostate tumor Lifibrol
(activator)
(1.14.99.9) **Atherosclerosis**
Nilutamide (launched), vorozole abiraterone, L-36, CB-7661, CB-
Hypercorticism 7645, 3-
and 4-pyridyl adamantanecarboxylates, YM-116, GI-
Cushing's syndrome 111924,
CB-7661, YM-55208,. . . Psoriasis 79787,
ZM-105180, AR-639
Platelet-derived growth factor Neoplasm
PD-171026, SU-4984, SU-5402, SU-1498, phenylamino-
receptor tyrosine kinase Psoriasis
pyrimidines, leflunomide, PD-089828, genistein, PD-090560,
(2.7.1.112) **Arteriosclerosis**
CEP-701, 4-(2-diethylaminoethoxy)-aminopyrido[2,3-

Carcinoma
d]pyrimidin-7(8H)-one, PD-171026, PD-151514, 7,8-dimethoxy-
Inflammation
5,10-dihydropyrimido [4,5-b]quinolin-4(1H)-one, CGP-52411, SU-
Restenosis 65847,
RPR-1015119, CGP-79787, SU-65786, SU-102, B-1146
Cardiovascular disease
compounds, KI-6896, CGP-53716, leflunomide, 3-(4-
Ovary tumor
Pyridinyl)quinolines, SU-6668
Brain tumor
Solid tumor
Prostate tumor
Glomerulonephritis
Basic fibroblast growth factor Neoplasm
PD-089828, PD-090560, CEP-701, 4-(2-diethylaminoethoxy)-
receptor tyrosine kinase **Cardiovascular** disease
aminopyrido[2,3-d]pyrimidin-7(8H)-one, PD-171026, PD-151514,
(2.7.1.112) Prostate tumor
7,8-dimethoxy-5, 10-dihydropyrimido[4,5-b]quinolin-4(1H)-one,
CGP-52411
, RG-8803, BP-42, SU-6668
Beta subunit of DNA-dependant Bacterial infection Rifampin,
rifabutin, **rifalazil**, T9, SPA-S-565
RNA polymerase
(2.7.7.6)
DNA polymerase DNA directed Digestive tract tumor KN-208,
aphidicolin, KM-043, netivudine, A-79296, BMS-
(2.7.7.7) Carcinoma 181165,
E-EBU-dM, BMS-200475, MPC-531,. . .
DETD . . . Zanamivir, GS4104
(3.2.1.18)
Angiotensin-converting enzyme Hypertension
Captopril, fentiapril, pivalopril, zofenopril, alacepril, enalapril,
(3.4.15.1) Left ventricular systolic dysfunction
lisinopril, benazepril, quinapril, moexipril, ramipril, spirapril,
Myocardial infarction
perindopril, indolapril, pentopril, indalapril, cilazapril, fosinopril,
Scleroderma renal crisis
CGS-30440, ceronapril, zabiciprilat, RB-106, temocapril,
Heart failure
trandolapril, mixanpril, MDL-102769, benzofused macrocyclic
Diabetic neuropathy lactams,
sampatrilat, UK-79942, UK-63831, CGP-28106, BMS-
Pain 182657,
MDL-100240, AB-47, moveltipril, imidapril, RB-105,
Opiate use disorder ER-32897,
ER-32935, CGS-27025, DU-1777, Z-13752A, Sch-
Cerebrovascular ischemia
54470, ER-32945, BMS-189921, MDL-27088, BRL-36378,
libenzapr
il, utibapril, synecor, quinaprilat, RB-101, RB-120, FPL-
66564,
delapril, moexiprilat, SC-50560, prentyl, MDL-27467A,
RL-6134,
idrapril, cyclic diazepinones, fasidotril, GI-155704A,
zofenopri
l, CGS-26670, SA-7060, omapatrilat
Thrombin Anti-coagulation Heparin,
low molecular weight heparin, DHG, argatroban,

(3.4.21.5) **Angina**
desirudin, bivalirudin, CVS-1123, BCH-1710, DuP-714, inogatran, Blood clotting disorder CVS-995, LY-293435, theromin, TRI-50b, LY-303496, SR- **Cerebrovascular** disease 80027A, RWJ-50353, melagatran, L-371912, bufrudin, TRI-166, Deep vein thrombosis LR-D/009, SD-523, BCH-2763, UK-156406, L-372460, Myocaridal infarction diarylsulfonamides, L-373890, UK-239326,. . . DX-9065A, arylsulfonamidopiperazine, 2,3-
(3.4.21.6) Deep vein thrombosis
disubstituted beta-alanines, Disseminated intravascular (tetrahydroisoquinolyloxy)phenylacetic acid derivatives, ZK- coagulation 805350, BX-807834, ZK-807191, C-92178, 2,4-diazepin-3-one **Myocardial** infarction derivatives, rTAP, Cordecin AS, SK-549, DHG, FX-2212, SEL- **Angina** 2711, yagin, BM-141248, ZK-806350, ZK-807191, SR-90107, Lung embolism KFA-1411, RPR-120844, SEL-2489, SEL-2711, SEL-1915, SEL- Thromboembolism 2219, danaparoid, heparin, Factorex, ardeparin, CY-222, **Cerebrovascular ischemia** benzamido-benzodiazepinone derivatives, YM-75466, RPR- 807834, BX-807834, ZK-805412, ZD-4927, antistatin, diarylsul fonamides, CVS-1578, CVS-1778, CVS-2097, BCH- 1710, YM-60828, L-375378, desmin 370, CVS-1801, LY-368052, GR-133487 , P-0933

Factor VIIa Thrombosis Bikunin,
NAP-B, NAPc2, plancinin, aprosulate, heparin
(3.4.21.21) Deep vein thrombosis
Disseminated intravascular coagulation
Myocardial infarction
Aneina
Lung embolism

TNF-alpha converting enzyme Arthritis GW-1988,
BB-2983, BB-3635, GW-3333, D-5410, CH-138, CH-
(TACE) Osteoporosis 175,
CH-263, marimastat analogs
(3.4.24) Inflammatory. . . renal tumor,
NU/ICRF-505, NSC-675967, AP-4010, CKD-602, camptothecin, stomach tumor, glioma, UCE-6,
DACA, cyclothialidine myeloproliferative disorder, lymphoma)

Ligase Enzymes
Unclassified Enzymes

Microsomal triglyceride transfer **Atherosclerosis**
BMS-197636, BMS-200150, BMS-192951, BMS-201038, GR-
protein Hyperlipidemia 328713,
4'-bromomethaqualone, 4'-bromo-3'- Hypercholesterolemia

methylmethaqualone
Hypertriglyceridemia
UDP-GlcNAc transferase Bacterial infection
Ramoplanin
(2.4.2.30)
DETD . . . the liver homogenates is measured according to the method described in Biochem. Pharmacol. 12 (1963) 1439-1441. The activity in the **brain** can be measured in **brain** homogenastes according to the method described in Biochem Pharmacol. 12 (1963) 1439-1441. Activity as an antidepressant can be evaluated by. . .
DETD [0205] The in vivo usefulness of compounds as **cardiotonic** agents is demonstrated by causing a significant increase in contractile force in the is olated cat atria and papillary muscle procedure and in causing a significant increase in **cardiac** contractile force in the anesthetized dog procedure with low or minimal changes in **heart** rate and blood pressure. These procedures are described in U.S. Pat. No. 4,072,746. Alternatively, guinea pig **heart** muscles can be used to monitor contractile response and the effect of **cardiac** contractility in anesthetized dogs can be measured according to U.S. Pat. No. 4,751,227. The effect on coronary and femoral blood. . .

L166 ANSWER 30 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2004:46788 USPATFULL
TITLE: High purity lipopeptides, Lipopeptide micelles and processes for preparing same
INVENTOR(S): Kelleher, Thomas J., Weston, MA, United States
Lai, Jan-Ji, Westborough, MA, United States
DeCourcey, Joseph P., Charlestown, MA, United States
Lynch, Paul, Arlington, MA, United States
Zenoni, Maurizio, Milan, ITALY
Tagliani, Auro, Pavia, ITALY
PATENT ASSIGNEE(S): Cubist Pharmaceuticals, Inc., Lexington, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6696412	B1	20040224	
APPLICATION INFO.:	US 2000-735191		20001128	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-177170P	20000120 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Low, Christopher S. F.
ASSISTANT EXAMINER: Kam, Chih-Min
LEGAL REPRESENTATIVE: Douros, Timothy J., Mandelblatt, Jill M. N.
NUMBER OF CLAIMS: 56
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 18 Drawing Figure(s); 11 Drawing Page(s)
LINE COUNT: 2480
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention discloses highly purified daptomycin and to pharmaceutical compositions comprising this compound. The invention discloses a method of purifying daptomycin comprising the sequential steps of anion exchange chromatography, hydrophobic interaction chromatography and anion exchange chromatography. The invention also discloses a method of purifying daptomycin by modified buffer enhanced anion exchange chromatography. The invention also discloses an improved method for

producing daptomycin by fermentation of Streptomyces roseosporus. The invention also discloses high pressure liquid chromatography methods for analysis of daptomycin purity. The invention also discloses lipopeptide micelles and methods of making the micelles. The invention also discloses methods of using lipopeptide micelles for purifying lipopeptide antibiotics, such as daptomycin. The invention also discloses using lipopeptide micelles therapeutically.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . of any organ or tissue in the body. These organs or tissue include, without limitation, skeletal muscle, skin, bloodstream, kidneys, **heart**, lung and bone. The method of the invention may be used to treat, without limitation, skin and soft tissue infections, . . .

DETD . . . KA 159, Dynemicin A, DX8739, DU 6681; Cefluprenam, ER 35786, Cefoselis, Sanfetrinem celexetil, HGP-31, Ceipirome, HMR-3647, RU-59863, Mersacidin, KP 736, **Rifalazil**; Kosan, AM 1732, MEN 10700, Lenapenem, BO 2502A, NE-1530, PR 39, K130, OPC 20000, OPC 2045, Veneprim, PD 138312, PD. . .

IT 54-85-3, Isoniazid 56-75-7, Chloramphenicol 58-14-0, Pyrimethamine 60-54-8, Tetracycline 65-49-6, Paraaminosalicylic acid 68-41-7, Cycloserine 74-55-5, Ethambutol 98-96-4, Pyrazinamide 104-06-3, Thiacetazone 154-21-2, Lincomycin 303-81-1, Novobiocin 443-48-1, Metronidazole 536-33-4, Ethionamide 738-70-5, Trimethoprim 751-94-0, Fusidate sodium 1400-61-9, Nystatin 1403-66-3, Gentamicin 1404-90-6, Vancomycin 1405-87-4, Bacitracin 1405-97-6, Gramicidin 1406-05-9, Penicillin 1406-11-7, Polymyxin 1695-77-8, Spectinomycin 2022-85-7, Flucytosine 5714-73-8, Methenamine hippurate 6998-60-3, Rifamycin 7681-93-8, Pimaricin 11003-38-6, Capreomycin 11006-76-1, Streptogramin 11076-17-8, Sordarin 11111-12-9, Cephalosporin 12633-72-6, Amphotericin 12650-69-0, Mupirocin 14222-60-7, Prothionamide 15318-45-3, Thiamphenicol 18323-44-9, Clindamycin 23155-02-4, Fosfomycin 32988-50-4, Viomycin 37517-28-5, Amikacin 51667-26-6, Oxazolidinone 56391-56-1, Netilmicin 61036-62-2, Teicoplanin 64221-86-9, Imipenem 65243-33-6 65277-42-1, Ketoconazole 65472-88-0, Naftifine 73090-70-7, Epiroprim 73384-59-5, Ceftriaxone 78110-38-0, Aztreonam 82800-75-7, Antibiotic A 21978 83200-96-8, Carbapenem 84625-61-6, Itraconazole 84957-29-9, Cefpirome 86386-73-4, Fluconazole 87638-04-8, Carumonam 91161-71-6, Terbinafine 99376-22-4 109545-84-8, Ziracin 111452-88-1, K130 113359-04-9, Cefozopran 116853-25-9, Cefluprenam 120410-24-4, Biapenem 120788-07-0, Sulopenem 122672-46-2, Cispentacin 122841-10-5, Cefoselis 124412-57-3, Dynemicin A 126602-89-9, Synercid 128104-18-7, Mersacidin **129791-92-0**, Rifalazil 129951-17-3, DU 6681 133686-28-9, KP 736 138126-04-2, BO 2502A 139637-11-9, PR 39 141611-76-9, Sanfetrinem sodium 141646-08-4, Sanfetrinem cilexetil 143158-16-1, PD 138312 143383-20-4, PD 140248 145078-62-2, MerWF3010 145260-69-1, CP 111905 147214-63-9, Cyclothialidine 149137-72-4, DX8739 149951-16-6, Lenapenem 154445-06-4, CL 331002 157542-49-9, CS-834 157998-96-4, Azoxybacilin 158295-97-7, TOC 39 161856-02-6, OCA-983 171099-57-3, LY 333328 176950-36-0, Micacocidin A 180462-26-4, Arthrichitin 180992-28-3, Khafrefungin 185377-91-7, LL 15G256γ 186319-97-1, ER 35786 188793-60-4, Antibiotic A 54145 191114-48-4, HMR 3647 194804-75-6, T 3811 195874-55-6, MEN 10700 199169-60-3, Corynecandin 205925-96-8, Sch 40832 224452-66-8, SB-275833 252188-71-9, Ro 65-5788 345631-66-5, Eveminomycin 345631-70-1, KA 159 345631-86-9, GV-143253 345631-92-7, A-99058.1 345631-93-8, A-165600 345631-94-9, A-179796 345631-96-1, HGP-31 345631-97-2, RU-59863 345631-98-3, Kosan 345631-99-4, AM 1732 345632-00-0, NE-153O 345632-01-1, OPC 20000 345632-02-2, OPC 2045

345632-44-2, Veneprim 345632-48-6, SEP-132613 345632-68-0, SR-15402
345632-69-1, SUN A0026 351496-61-2, LY 33328 351496-93-0, HMR 364
(purification of lipopeptides and lipopeptide micelles)

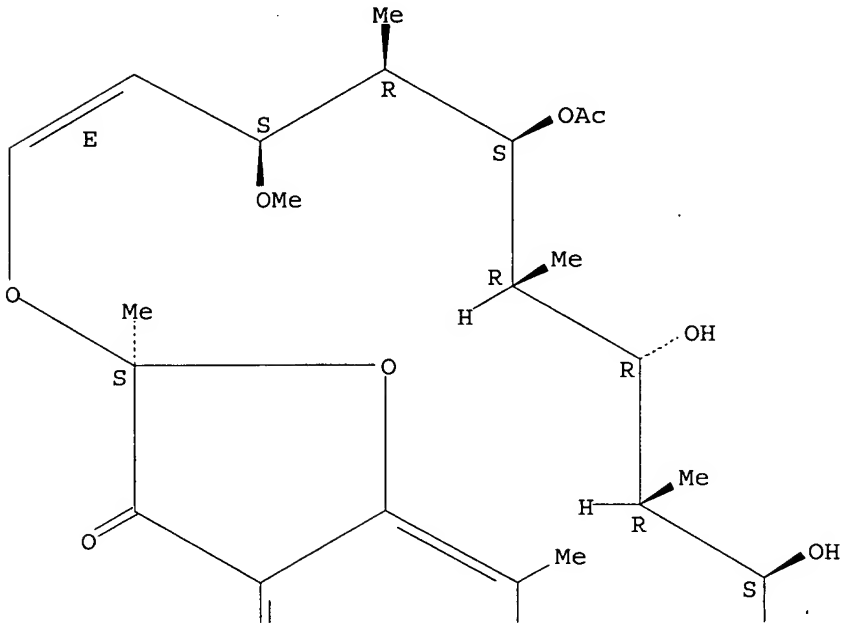
IT **129791-92-0**, Rifalazil
(purification of lipopeptides and lipopeptide micelles)

RN 129791-92-0 USPATFULL

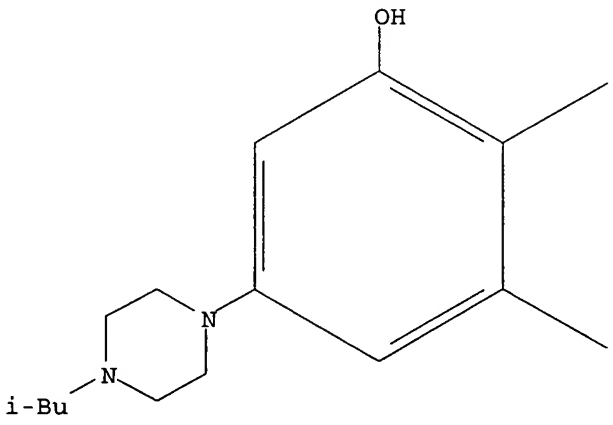
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

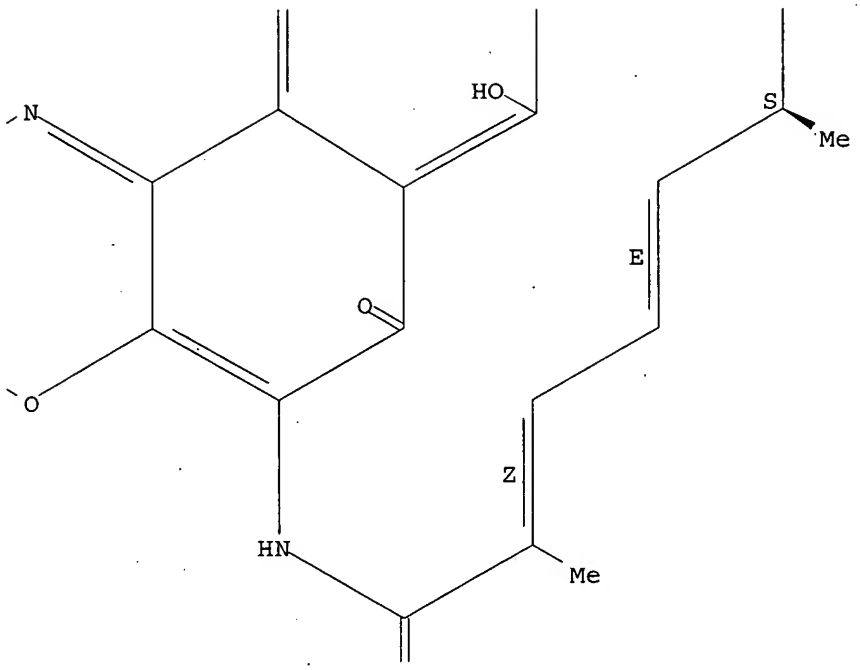
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

O

L166 ANSWER 31 OF 40 USPATFULL on STN

ACCESSION NUMBER:	2003:289144 USPATFULL
TITLE:	Method for treatment of bacterial infections with once or twice-weekly administered **rifalazil**
INVENTOR(S):	Rose, Lynn M., Seattle, WA, UNITED STATES Porubek, David J., Seattle, WA, UNITED STATES Montgomery, Alan B., Bellevue, WA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003203903	A1	20031030
APPLICATION INFO.:	US 2002-243141	A1	20020914 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-972320, filed on 5 Oct 2001, PENDING Continuation of Ser. No. US 1999-464353, filed on 15 Dec 1999, GRANTED, Pat. No. US 6316433

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-112921P	19981218 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	Hana Verny, PETERS, VERNY, JONES & SCHMITT LLP, Suite 6, 385 Sherman Avenue, Palo Alto, CA, 94306
NUMBER OF CLAIMS:	16

EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 10 Drawing Page(s)
LINE COUNT: 1792
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for treatment of bacterial infections with **rifalazil** administered once-weekly, or twice-weekly. A method for treatment of tuberculosis caused by Mycobacterium tuberculosis, infections caused by Mycobacterium avium complex, infections caused by Chlamydia pneumoniae and infections caused by Helicobacter pylori by administering to a patient suffering from the bacterial infection 1-100 mg of **rifalazil** once or twice a week. In this dose regimen, the treatment is fast, efficacious and eliminates undesirable secondary symptoms observed with daily doses of 1-50 mg of **rifalazil.**

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Method for treatment of bacterial infections with once or twice-weekly administered **rifalazil**

AB A method for treatment of bacterial infections with **rifalazil** administered once-weekly, or twice-weekly. A method for treatment of tuberculosis caused by Mycobacterium tuberculosis, infections caused by Mycobacterium avium complex,. . . pneumoniae and infections caused by Helicobacter pylori by administering to a patient suffering from the bacterial infection 1-100 mg of **rifalazil** once or twice a week. In this dose regimen, the treatment is fast, efficacious and eliminates undesirable secondary symptoms observed with daily doses of 1-50 mg of **rifalazil.**

SUMM [0003] The current invention concerns a method for treatment of bacterial infections with **rifalazil** administered once-weekly or twice-weekly. In particular, the invention concerns a method for treatment of tuberculosis caused by Mycobacterium tuberculosis, infections. . . caused by Chlamydia pneumoniae and infections caused by Helicobacter pylori by administering to a patient suffering from the bacterial infection **rifalazil** once or twice a week. In this dose regimen, the treatment is fast, efficacious and eliminates undesirable secondary symptoms observed with daily doses of 1-50 mg of **rifalazil.**

SUMM . . . Chlamydia pneumoniae and H. pylori infections with once a week or twice a week administration of a relatively new antibiotic, **rifalazil**, that belongs to the class of antibiotics called ansamycins. **Rifalazil** has the same or better activity than either rifabutin or rifampin, the other two antibiotics of the same class and. . . H. pylori when administered only once a week or twice a week in doses from 1 to 50 mg. Previously, **rifalazil** has been administered on daily basis and because of the severe secondary adverse reactions, was discontinued as a drug for. . .

SUMM [0010] **Rifalazil** compound has been described in the U.S. Pat. No. 4,983,602 where its antibacterial activity has been disclosed. Dosages described in. . . when clinical trials with these doses of the antibiotic were administered daily, many adverse reactions occurred and the treatment with **rifalazil** was discontinued.

SUMM . . . One aspect of the current invention is a method for treatment of bacterial infections with once or twice-week administration of **rifalazil.**

SUMM [0013] Another aspect of the current invention is a method for treatment of tuberculosis with once or twice-week administration of **rifalazil.**

SUMM . . . of the current invention is a method for treatment of Mycobacterium avium complex infections with once or twice-week administration of **rifalazil.**

SUMM . . . aspect of the current invention is a method for treatment of

Chlamydia pneumoniae infections with once or twice-week administration of **rifalazil.**

SUMM . . . aspect of the current invention is a method for treatment of Helicobacter pylori infections with once or twice-week administration of **rifalazil.**

DRWD . . . blood cells counts in daily dosing regimen used in a clinical trial on human volunteers where the daily dose of **rifalazil** was 5 or 25 mg compared to a control group receiving placebo.

DRWD . . . blood cells count in daily dosing regimen used in a clinical trial on human volunteers wherein the daily dose of **rifalazil** was 25 mg.

DRWD . . . blood cells count in daily dosing regimen used in a clinical trial on human volunteers wherein the daily dose of **rifalazil** was 5 mg.

DRWD . . . human volunteers where the daily dose was 5 or 25 mg compared to a control group which received placebo without **rifalazil.**

DRWD . . . in absolute neutrophil count in daily dosing regimen used in a clinical trial on human volunteers wherein daily dose of **rifalazil** was 25 mg.

DRWD . . . in absolute neutrophil count in daily dosing regimen used in a clinical trial on human volunteers wherein daily dose of **rifalazil** was 5 mg.

DRWD [0023] FIG. 7 illustrates changes in platelets counts after 20 daily administration of 5 and 25 mg **rifalazil** to healthy volunteers in a clinical trial compared to a control group receiving placebo.

DETD [0027] "**Rifalazil**" means 3'-hydroxy-5'-(4-isobutyl-1-piperazinyl)benzoxasinorifamycin also known as **KRM-1648.**

DETD [0044] "EKG" means **electrocardiogram.**

DETD . . . confirmation in vitro, in vivo and in clinical trials that once-a-week or twice-a-week doses of 1-100, preferably 1-50 mg of **rifalazil** effectively treats bacterial infection without adverse reactions and without undesirable secondary symptoms observed with daily administration of this drug.

DETD [0084] Although **rifalazil** was found to be effective against mycobacterium species, it has never been used as a therapeutic agent for treatment of mycobacterial diseases because at the daily dose regimen which was thought to be necessary to its efficacious antibacterial activity, **rifalazil** caused severe adverse reactions and secondary symptoms. The adverse reactions included flu-like symptoms with severe headache, malaise, fever, back pain, myalgia, chills, dizziness, nausea, vomiting, body pain and weakness. Additionally, the daily administration of **rifalazil** resulted in changes in blood cell counts, particularly in decrease of white blood cells counts (leukopenia), absolute neutrophil count and platelet count as well as in decreased blood hemoglobin. For these reasons, clinical studies involving daily dosing of **rifalazil** were abandoned.

DETD [0085] It has now been found and is a subject of this invention that **rifalazil** in once-a-week or at most twice-a-week dosing regimen is effective in eradication of Mycobacterium tuberculosis, Mycobacterium avium complex, Chlamydia pneumoniae. . .

DETD [0087] **Rifalazil** and its related drugs rifampin and rifabutin, all belonging to a group collectively described as rifamycins, were known to exhibit. . .

DETD [0088] A. Physical, Chemical and Pharmaceutical Properties of **Rifalazil**

DETD [0089] **Rifalazil** is 3'-hydroxy-5'-(4-isobutyl-1-piperazinyl) benzoxasinorifamycin of the chemical structure ##STR1##

DETD [0090] **Rifalazil** is a member of the rifamycins, a complex group of antibiotics originally isolated from **Nocardia**

mediterranei that exhibits antimicrobial activity against Mycobacterium spp. The rifamycins belong to a class of antibiotics called ansamycins, which contain. . .

DETD [0091] **Rifalazil** is a nonpolar molecule that is stable and essentially insoluble in water. Two chemically-related drug substances rifampin and rifabutin are. . .

DETD [0092] **Rifalazil** synthesis is disclosed in U.S. Pat. No. 4,983,602, incorporated herein by reference in its entirety. Its known in vitro and. . . Recent Res. Devel. Antimicrob. Agents Chemother., 2:37 (1997), incorporated herein by reference. While these studies confirm the antibacterial activity of **rifalazil** in vivo as well as in vitro, such activity is based on daily administration of 2.5 and 5 mg of the drug to the mice infected with M. tuberculosis, corresponding to about 175 or 350 mg **rifalazil** dose/day/70 kg human.

DETD [0093] Additionally, in vivo studies were performed where the therapeutically effective doses of **rifalazil** and rifampin were given at various intervals. When the dose 10 mg/kg (corresponding to 700 mg/70 kg human) six times. . . reduction in CFU. However, the used and documented doses were extremely and unphysioloqically high. For humans, the daily dose of **rifalazil** above 300 mg is unphysiological and even 50 mg of **rifalazil** administered to humans daily causes severe adverse reactions.

DETD [0095] **Rifalazil** was extensively tested in vitro and in vivo in animal models and compared to other ansamycins, rifampin and rifabutin. The. . .

DETD [0097] In vitro studies show that **rifalazil** acts on bacterial DNA-dependent RNA polymerase and inhibits the growth of aerobic and anaerobic gram-positive bacteria. However, **rifalazil** is relatively inactive against gram-negative bacteria. This spectrum of activity is similar to rifampin and rifabutin, two related drugs.

DETD [0098] **Rifalazil** is a potent inhibitor of many mycobacterium spp., including the M. tuberculosis (MTB) and M. avium complex (MAC), Chlamydia pneumoniae. . . depending on the degree of resistance to rifampin. When tested side by side against the same strains, the activity of **rifalazil** in vitro is consistently greater than either rifabutin or rifampin. Minimum bactericidal concentrations (MBCs) are typically 2-4 fold higher than. . .

DETD [0099] The efficacy of **rifalazil** have been examined in vivo in macrophage and in animal models. **Rifalazil** readily accumulates in human macrophages and is bactericidal at concentrations equivalent to the MBCs established in vitro. In animal models of MTB infection, **rifalazil** was the most active single-agent against organisms in the spleen and lungs, although the combination of **rifalazil** and isoniazid (INH) or **rifalazil** and pyrazinamide (PZA) was more effective against organisms in the lung than either drug alone (Antimicrobial Agents Chemotherapy, 40: 298. . .

DETD [0100] The therapeutic effects of **rifalazil** are also long-lasting. For example, in mice infected with M. intracellulare, **rifalazil** significantly reduced the number of colony forming units (CFUs) in organs after four and eight weeks of treatment and did so to a greater extent than rifabutin or rifampin. In a rabbit model of M. avium infection, **rifalazil** also reduced the bacterial load on organs compared to controls. Treatment of MTB infection in mice with **rifalazil** and INH for 12 weeks completely sterilized the lungs and spleens of infected animals and eliminated regrowth of the organisms. . .

DETD [0101] In chronic studies with dogs and rats, the no-observed-adverse-effect-level was 1000 mg/kg. The absolute bioavailability of .sup.14C-**rifalazil** in rats at a dose of 3 mg/kg was 30 to 40%, but was

reduced at higher doses. **Rifalazil** was slowly eliminated from the blood (mean terminal half-life of 12.5 hr) with a mean systemic clearance (CL/F) of 0.184. . .

DETD [0102] 2. **Rifalazil** Antibacterial Activity in vitro

DETD [0103] The antimicrobial activity of **rifalazil** was measured in vitro against a variety of bacterial species. In vitro studies show that **rifalazil** inhibits the bacterial growth of aerobic and anaerobic gram-positive bacteria, but is relatively inactive against gram-negative bacteria. **Rifalazil** inhibits the growth of many Mycobacterium spp. (Antimicrobial Agents Chemotherapy, 35:542 (1991)), particularly the slower growing mycobacteria such as M. tuberculosis, M. avium, and M. intracellulare. Based on MIC.sub.90 comparisons, as seen in Table 1, **rifalazil** was more active than rifampin.

TABLE 1

MIC.sub.90 and Rifampin Against Mycobacterium spp

Species	No. Of Strains	MIC.sub.90 (μg/mL) **Rifalazil**	Rifampin
M. intracellulare	31	0.1	12.5
M. avium	18	1.56	100
M. tuberculosis	22	12.5	100

*MIC determined by agar dilution. . .

DETD [0104] The in vitro activity of **rifalazil** against M. tuberculosis has been determined by measuring the minimum inhibitory concentration (MIC) for a variety of clinical isolates and. . . reference strains. The results of these studies are summarized in Table 2.

TABLE 2

Summary of In Vitro Susceptibility Studies for **Rifalazil**

Ref.	MIC Method	No. Of Strains.sup.1	MIC Range (μg/mL)	MIC.sub.90 (μg/mL)
1	BACTEC	30 (rif.sup.r and rif.sup.s)	≤0.002 to 4.0.sup.	2.0
2	BACTEC. . .			

DETD [0106] As seen in Table 2, **rifalazil** is more active than 25 rifampin based on MIC.sub.90 comparisons, however, the spectra of its antibacterial activities are similar to. . .

DETD [0107] The in vitro activity of **rifalazil** against M. tuberculosis has been determined by measuring the minimum inhibitory concentration (MIC) for a variety of clinical isolates and. . .

DETD [0108] Studies described in Antimicrobial Agents, Chemotherapy, 39: 2295, (1995) determined the MICs of **rifalazil** against thirty clinical isolates and two stock cultures (H37Rv and Kurono) of M. tuberculosis (Table 3).

TABLE 3

MIC of **Rifalazil**, Rifabutin and Rifampin

Drug	MIC (μg/mL).sup.1 for Clinical Isolates.sup.2 MIC50 50% inhibition	MIC90 90% inhibition	Reference M. tuberculosis strain H37Rv	Kurono
Rifalazil	0.016	2.0	0.004	0.002

Rifabutin	0.063	8.0	0.016	0.016
Rifampin	4.0	>128.0	0.125	0.063

.sup.1MICs were determined by BACTEC method.
.sup.2Thirty strains were. . .

DETD [0109] Table 3 shows Minimum Inhibitory Concentrations (MICs) of **rifalazil**, rifabutin and rifampin for clinical isolates and two reference strains of Mycobacterium tuberculosis.

DETD [0110] As seen in Table 3, **rifalazil** had more than a 64-fold greater activity than rifampin and a 4-fold greater activity than rifabutin based on comparisons of the MIC.sub.50 and MIC.sub.90. This increased activity of **rifalazil** was also observed with the reference strains. An examination of the individual MICs of the thirty isolates shows that **rifalazil** was more active than rifamipin in all thirty isolates and more active than rifabutin in twenty-eight isolates.

DETD [0111] The MIC and NBC of **rifalazil** against extracellular M. tuberculosis and M. tuberculosis in human macrophages using strains H37Rv, Erdman, and Atencio were described in Antimicrobial Agents, Chemotherapy, 409:1482 (1996). Extracellular and intracellular bacteria were exposed to varying concentrations of **rifalazil** for 7 or 8 days, macrophages were lysed where applicable, then the-CFUs were determined by plating on agar. The MIC was defined as the lowest concentration of **rifalazil** that inhibited more than 99% of the growth following the drug-incubation period. The MBC was defined as the lowest concentration of **rifalazil** that killed more than 99% of the bacteria following the drug-incubation period. The results of the study show that the MIC and MBC of **rifalazil** are at least 10-fold lower than rifampin for both intracellular and extracellular bacteria (Table 4).

TABLE 4

Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC) of **Rifalazil** and Rifampin (RMP) Against Mycobacterium tuberculosis Strains

	Concentration (μg/mL)							
	Intracellulare Bacteria				Extracellular Bacteria			
	Rifalazil		Rifampin		**Rifalazil**			
Strain	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
H37Rv	0.004	0.016	0.25	1.0	0.008	0.031	0.12	0.5
Erdman	0.008	0.008	0.12.	. .				

DETD [0113] 3. **Rifalazil** Antibacterial Activity in vivo

DETD [0114] The therapeutic effect of **rifalazil** was examined by measuring gross lung lesions, bacterial loads, and survival time in mice infected with M. tuberculosis and subsequently treated with **rifalazil** or rifampin for eight weeks (Antimicrobial Agents, Chemotherapy, 39: 2295 (1995)). In each of these tests, **rifalazil** outperformed rifampin in treating the disease.

DETD [0115] The activity of **rifalazil** alone and in combination with other drugs in mice infected with the rifampin-sensitive M. tuberculosis strain Erdman (MIC.sub.rif=0.06 kg/mL) was. . .

DETD [0116] Initial experiments compared the ability of **rifalazil**, rifabutin, or rifampin (all at 20 mg/kg) to reduce the bacterial load in lungs and spleens of infected mice compared to untreated mice. **Rifalazil** reduced bacterial loads to a significantly greater extent than the other two drugs ($P<0.01$). No significant differences were observed between. . .

DETD [0117] Additional experiments examined the ability of **rifalazil** (20 mg/kg) alone and in combination with INH (isoniazid, mg/kg), PZA (pyrazinamide, 150 mg/kg), EMB (ethambutol, 125 mg/kg), or LEV. . .

DETD . . . reduced CFUs in the spleen compared to controls, except for PZA. PZA did not significantly reduce CFUs compared to controls. **Rifalazil** was the most active single-agent against organisms in the spleen. only the combination of **rifalazil** plus PZA was more active than **rifalazil** alone.

DETD [0119] In lungs, treatment with **rifalazil** or INH significantly reduced cell counts in lungs compared to early controls. Compared to late controls, treatment with **rifalazil**, INH, EMB, or LEV reduced cell counts in lungs. **Rifalazil** was the most active single-agent. The combinations of **rifalazil** plus INH or **rifalazil** plus PZA were more active against organisms in lungs than treatment with **rifalazil** alone.

DETD . . .) 12 weeks and the regrowth of organisms in spleen and lung was measured for 24 weeks post-treatment. The combination of **rifalazil** (20 mg/kg) and INH (25 mg/kg) was significantly more effective at reducing the number of CFUs in spleens and lungs of mice compared to **rifalazil** alone (20 mg/kg), INH alone (25 mg/kg), rifampin alone (20 mg/kg), and the combination of rifampin and INH (20 mg/kg. . .

DETD [0122] **Rifalazil** activity was also tested on other bacteria and organisms. **Rifalazil** shows a strong antibacterial activity against Chlamydia pneumoniae and against Helicobacter pylori.

DETD [0123] Sensitivity testing was conducted in cell cultures against Chlamydia pneumoniae strain TW-1 83 using **rifalazil**, clanthromycin, or azithromycin. In these studies, **rifalazil** was 300-fold more potent than clanthromycin and 1500-fold more potent than erythromycin. The in vivo testing of **rifalazil** used a mouse model infected with Chlamydia pneumoniae strain AR-39. The results showed that Chlamydia pneumoniae was not detectable from the lungs of an animal five days after the cessation of **rifalazil** treatment by intraperitoneal injection of **rifalazil** at 1 mg/kg QID for three days. All control animals remained infected.

DETD [0124] **Rifalazil** bactericidal activities were also evaluated in vitro against twenty-four strains of Helicobacter pylori. In these studies, **rifalazil** exhibited more potent antimicrobial activities against Helicobacter pylori than amoxicillin and rifampin. Time-kill studies, described in Abstract, 4th Japan-Korea International. . . Symposium on Microbiology, Takashimaya, Japan, October 22-23 (1998), revealed that the CFUs at 24 hours in the broth medium containing **rifalazil** at 0.04 mg/mL were more than 4.5 log lower than the control at zero hours, indicating **rifalazil**'s potent bactericidal activity. Under the same conditions amoxicillin at 0.31 mg/mL produced only 1 log decrease in CFU/mL after 24. . .

DETD [0125] Results described above indicate that **rifalazil** has very good antibacterial activity and is a better choice of the drug for treatment of bacterial infections caused by. . .

DETD [0126] 5. Pharmacology of **Rifalazil**

DETD . . . studies were undertaken in mice, rats, and dogs, and in isolated guinea pig ileum. The preclinical pharmacology data showed that **rifalazil** has no important central/autonomic nervous system, respiratory, **cardiovascular**, digestive system, or renal pharmacological effects.

DETD [0128] **Rifalazil** had little effect on the clinical signs or general behavior of mice following oral administration of 100, 300, or 1,000 mg/kg. **Rifalazil** had no effect on the spontaneous locomotor activity of mice at 100 and 300 mg/kg. At 1000 mg/kg, **rifalazil** caused an increase in spontaneous locomotor activity

for one hour.

DETD [0129] 6. Pharmacokinetics of **Rifalazil**

DETD . . . based upon those utilized in the single and multiple-dose toxicology studies. In addition, the absorption, distribution, metabolism, and elimination of **rifalazil** was studied in rats and dogs. These studies confirmed prior findings that there are species differences vis-a-vis sensitivity to and response to treatment with **rifalazil.**

DETD [0131] Preclinical pharmacokinetic data in rats and dogs showed that the disappearance of **rifalazil** and/or metabolites from whole blood is slow and that significant whole blood concentrations can be achieved following repeated oral administration. Upon repeated dosing, a slight increase in **rifalazil** C.sub.max and AUC values was observed in rats and dogs. Such increase was consistent with the drug accumulation. Significant metabolism of **rifalazil** through deacetylation in both dogs and rats and hydroxylation in dogs only, occurred in both single and multiple-dose studies. In addition, significant accumulation of both metabolites was observed following repeat **rifalazil** dosing in dogs.

DETD [0132] 7. Toxicology of **Rifalazil**

DETD [0134] Under the conditions of these studies, **rifalazil** was relatively well-tolerated in animal models following single or multiple-dose oral administration. Hematological changes were noted following a multiple-dose oral. . .

DETD . . . lymphocytes. Lymphoid depletion in the spleens of treated animals and decreased peripheral blood lymphocyte count show that at certain concentration, **rifalazil** causes adverse reactions. However, there was no evidence that the animals in this study were immunosuppressed, as no opportunistic infection. . .

DETD [0136] The 13-week study of daily oral administration of **rifalazil** to dogs demonstrated that the "no observable adverse effect level" was considered to be 300 mg/kg for dogs. Lower lymphocytic. . .

DETD . . . that there is clear species difference in adverse reactions response between animals and humans. While in mice, rats and dogs **rifalazil** dosages over 300 mg/kg were well tolerated in long-term studies, such tolerance was not found in human volunteers. The dose. . .

DETD [0141] A. Safety, Pharmacokinetics and Toxicity of **Rifalazil** in Healthy Volunteers

DETD [0143] A total of four clinical trials have been conducted to study the effects of **rifalazil** in humans. Two single-dose Phase 1 clinical trials (001) and (002) assessed the safety and pharmacokinetics of **rifalazil** in normal, healthy, fasted subjects. In the 001 trial, a single 300 mg dose of **rifalazil** was administered to six subjects. In the 002 trial, single doses of 30 mg or 100 mg were administered to. . .

DETD . . . (003) and fourth (004) Phase 1 clinical trials were multiple-dose studies. Because evidence from animal studies showed increased bioavailability when **rifalazil** was administered with food, the clinical trials were designed to further assess the safety and pharmacokinetics of **rifalazil** in fed, normal, healthy subjects.

DETD . . . Subjects were divided into two groups. In Group 1, eight subjects were randomized to a daily 25 mg dose of **rifalazil** and four subjects were randomized to placebo. Numerous adverse reactions began to appear with the 25 mg dose several days. . . of 5 mg in group 2. Group 2 consisted of eight subjects randomized to a daily 5 mg dose of **rifalazil** and four subjects randomized to placebo.

DETD . . . trial (004) was a also a randomized, rising, double-blind,

multiple-dose, placebo-controlled study. In this trial, weekly doses of placebo or **rifalazil** (25 mg or 50 mg) were administered to the subjects for a total of 4 weeks. All subjects received the. . . for an additional 14 days after the last dose. Four subjects were randomized to placebo, six subjects to 25 mg **rifalazil**, and eight subjects to 50 mg **rifalazil.**

DETD . . . and severity of adverse reactions, and the time to resolution. Safety was assessed by physical examination, monitoring vital signs and **cardiac** function, measurement of clinical laboratory values in blood, serum, and urine, and by documenting adverse reactions. Systemic drug levels were. . .

DETD [0148] 2. Adverse Reactions Observed After **Rifalazil** Administration to Healthy Subjects

DETD [0152] In the first (001) and second (002) clinical trials, adverse reactions, change in laboratory parameters and pharmacokinetic of **rifalazil** were observed in healthy volunteers receiving dosages of 30 mg, 100 mg and 300 mg of **rifalazil.**

DETD . . . reactions with the 300 mg dose compared to the 30 and 100 mg doses.

TABLE 5

Adverse Reactions in Healthy Volunteers

		Rifalazil Study				
		001	002			001 and 002
		Dose				
Body System.sup.1	Adverse Reactions	300 mg n. . . 1	0 mg	30 mg 4	100 mg	All Doses
	Malaise	1	0	0	0	1
	Pain	1	0	0	0	1
CV	Tachy-**cardia**	3	0	0	0	3
	Vasodi-lation	0	1	1	1	3
DIG	Abnormal Stools	1	0	0	0	1
	Anorexia	1	0	0	0	1
. . .	0 1					
	Sweating	1	0	0	0	1
SS	Taste Prevision	1	0	0	0	1

.sup.1BODY: body as a whole; CV: **cardiovascular** system; DIG: digestive system; NER: nervous system; RES: respiratory system; SKIN: skin and appendages; SS: special senses.

DETD [0155] As seen in Table 6, 300 mg dose of **rifalazil** resulted in forty-one mild, eight moderate and four severe adverse reactions. In contrast, placebo, 30 or 100 mg doses resulted. . .

DETD . . . were decreased in a dose-dependent manner. These parameters returned to the normal range within 14 days of final administration of **rifalazil**, and were noted to be similar to effects produced by other rifamycins.

DETD [0158] The pharmacokinetics of **rifalazil** in whole blood in these two clinical trials was similar to that of **rifalazil** pharmacokinetics in plasma. Converse to data generated from animal studies, human subjects demonstrated a higher (1.6:1) plasma to blood ratio. Therefore, future pharmacokinetic analyses focused on **rifalazil** concentrations in plasma. Table 7 summarizes noncompartmental parameters derived from plasma concentrations in fasted subjects following administration of single doses of 30 mg, 100 mg, or

300 mg of **rifalazil** in these studies.

TABLE 7

Comparison of Noncompartmental Pharmacokinetic Parameters Derived from Plasma Concentrations in Single Dose Studies 001 and 002

Parameters (mean)	Trial and Dose **Rifalazil** - 001 300 mg	**Rifalazil** - 002 100 mg	30 mg
Tmax (h)	3.0	4.0	3.1
Cmax (ng/mL)	115.7	53.6	17.8

. . .

DETD [0160] In the third (003) and fourth (004) clinical trials, adverse reactions, change in laboratory parameters and pharmacokinetics of **rifalazil** were observed.

DETD . . . in clinical trails 003 and 004 appears in Table 8.

TABLE 8

Adverse Reactions in Single-Dose and Multiple Dose Trials

Body System.sup.1	Adverse Reactions	Study **Rifalazil**-003 5 mg/day (n = 8)	25 mg/day (n = 8)	**Rifalazil** 25 mg/wk	50 mg/wk	**Rifalazil**-003/004 0 mg	-004 All Doses
	. . . Pain	0	0	5	3	0	2
	Taste Perversion	0	2	0	0	0	2

.sup.1BODY body as a whole. CV **cardiovascular** system; DIG. digestive system; MS musculo-skeletal system, NER. nervous system. RES: respiratory system. SKIN skin and appendages. SS. special senses

DETD . . . trials. All these adverse reactions are considered "flu-like" symptoms.

TABLE 9

Adverse Reactions Observed in 003 and 004 Clinical Trials

Adverse Reactions	Study **Rifalazil** 003 0 mg (Placebo)	5 mg/ day	25 mg/ day	All doses	**Rifalazil** 004 0 mg (Placebo)	25 mg/	50 mg/
. . .							

DETD . . . headache and back pain, observed in the clinical trial 003 where the drug was administered daily. When the multiple-dose of **rifalazil** 25 mg/weekly was administered, the number of adverse reactions in the same dose regimen (25 mg) decreased substantially from thirteen. . . .

DETD . . . clinical trial 003 are compared to clinical trial 004, in terms of the adverse reactions associated with daily dosing of **rifalazil**. In Tables 10 and 11, the number of drug-related adverse reactions and severity of these reactions associated with daily dosing. . .

DETD [0166] As seen in Table 10, at daily dosing with 25 mg of **rifalazil**, subjects experienced total of one hundred and twelve

adverse reactions while at the daily dose of 5 mg, 8 subjects. . . total of fifty-two adverse reactions. Placebo groups experienced only one adverse reaction each. This study clearly show that multiple-dosages of **rifalazil** are dose dependent and that even a relatively small dosage of 5 mg of **rifalazil** daily cause substantial increase in adverse reactions compared to placebo.

DETD . . . in Table 11, severity of the adverse reactions was also dose-dependent. When the dosage of 25 or 5 mg of **rifalazil** was administered daily, one hundred and two and forty-six mild adverse reactions and ten and six moderate adverse reactions were. . .

DETD . . . at least one adverse reaction, compared to one of four placebo subjects. By Day 7, five subjects continued to receive **rifalazil** while three subjects dropped from the study because of adverse reactions. By Day 10, only one subject was still receiving drug. Dosing was suspended after Day 11 by the site investigator. Daily administration of **rifalazil** was, therefore, found to be unacceptable to the subjects and such daily administration had to be discontinued.

DETD . . . per patient was also about half the number in Group 2 versus Group 1. Five of the eight subjects receiving **rifalazil** completed the study. Three subjects dropped due to adverse reaction. One subject experienced half of all the recorded adverse reactions. . . adverse reactions that were graded moderate in severity within Group 2 (Table 11). Although three of the eight subjects receiving **rifalazil** reported a mild, "flu-like" symptoms, only one of these subjects discontinued the study early. All three subjects experiencing the "flu-like". . .

DETD [0172] In clinical trial 004, specifically, the adverse reactions associated with weekly dosing of **rifalazil** are listed in Tables 8 and 9, and compared to 003 trial results. Tables 12 and 13 show the number and severity of drug-related adverse reactions associated with once-a-week administration of **rifalazil** vis-a-vis each subject and each dose in 004 clinical trial.

TABLE 12

Number of Adverse Reactions in 004 Clinical Trial

Number. . .

DETD [0173] As seen in Table 12, the number of adverse reactions observed following once-a-week administration of **rifalazil** to healthy volunteers was directly related to the dosage of **rifalazil** administered. When the dosage was 25 mg/week, there were forty-six adverse reactions. When the dosage was 50 mg/week, then there. . .

DETD [0175] Details of the adverse reactions associated with weekly dosing of **rifalazil** appear in Tables 8, 9, 12 and 13. All eighteen subjects completed the 004 clinical trial. Fewer unique adverse reactions. . .

DETD . . . measurement remained within the normal established ranges. In clinical trial 003, all subjects in Group 1 receiving 25 mg of **rifalazil**/day discontinued the study early.

DETD . . . plots of white blood cell (WBC) counts of healthy volunteers receiving dosages 0 mg, 5 mg and 25 mg of **rifalazil** administered daily. Normal range of white blood cell counts, shown in the FIG. 1 as "L" and "H" lines, is. . .

DETD [0180] FIG. 2 shows individual white blood cell counts in healthy volunteers (Group 1) receiving 25 mg of **rifalazil** daily for 14 days. As seen in FIG. 2, subjects in Group 1 experienced a larger drop in WBC counts,. . .

DETD [0181] FIG. 3 shows individual white blood cell counts in healthy volunteers (Group 2) receiving 5 mg of **rifalazil** daily for 14

days. As seen in FIG. 3, subjects in Group 2 experienced lower decreases in WBC counts which. . .

DETD . . . shows mean absolute neutrophil count in twenty-four healthy volunteers following administration of 0 mg, 5 mg and 25 mg of **rifalazil** daily for 14 days. As seen in FIG. 4, the absolute neutrophil count results have shown less consistent patterns making. . .

DETD [0183] FIGS. 5 and 6 show individual absolute neutrophil counts in Group 1 receiving 25 mg of **rifalazil** daily for 14 days and Group 2 receiving 5 mg **rifalazil** daily for 14 days, respectively. Four subjects in Group 1, receiving 25 mg of **rifalazil**, seen in FIG. 5, and 3 subjects in Group 2, receiving 5 mg of **rifalazil** , seen in FIG. 6, experienced ANC values <2.0+10.sup.3/mm.sup.3, however no ANC value fell below <1.0+10.sup.3/mm.sup.3for any individual subject.

DETD . . . in FIG. 7, demonstrated small changes relative to placebo, with fewer changes occurring in the group receiving 5 mg of **rifalazil** versus the group receiving 25 mg. All hematologic parameters returned to normal within 14 days following administration of the last. . .

DETD . . . mean white blood cell plots for once a week dosage of 0 mg (control), 25 mg and 50 mg of **rifalazil** for four weeks. The subjects' hematological parameters were followed for an additional two weeks up to day 36.

DETD [0187] When the results seen in FIG. 8 (once-a-week administration of 50 and 25 mg **rifalazil**) are compared to results seen in FIG. 1 (once-a-day administration of 5 and 25 mg of **rifalazil**), the differences in WBC counts are readily observed. In FIG. 1, both 50 and 25 dosages show continuous drop in. . .

DETD . . . FIG. 9 shows mean absolute neutrophil counts for once-a-week dosage of 0 mg (control), 25 mg and 50 mg of **rifalazil** administered for four weeks. As above, subjects ANC were followed up to day 36. Three subjects in the 25 mg. . .

DETD [0189] FIG. 10 shows mean platelet plots for once-a-week dosage of 0 mg (control), 25 mg and 50 mg of **rifalazil** for four weeks with follow up to day 36. As seen in FIG. 10, once a week dosages of **rifalazil** on platelets were unremarkable without any observable changes outside of the normal range 150-450 K/CU MM.

DETD [0191] Pharmacokinetic analyses associated with clinical trials involved measurement of concentrations of **rifalazil** in plasma and/or whole blood of subjects participating in the four Phase 1 studies using high performance liquid chromatography. Most. . .

DETD . . . the 003 clinical trial and in Table 15 for the 004 clinical trial 004. Several pharmacokinetic patterns were consistently observed. **Rifalazil** appears to be slowly absorbed, widely distributed, and slowly eliminated via a multi-phasic process. Inter-patient variability was demonstrated.

DETD [0193] Due to extremely low levels of **rifalazil** measured in the urine, elimination of **rifalazil** seems to be non-renal, and probably occurs by the fecal route. In addition, low levels of oxidative metabolites of **rifalazil** were found in plasma. This further suggests that drug is excreted in the feces either in unchanged form or as. . .

DETD . . . 22). Because of extensive sampling after the fourth dose, this study yielded the most complete data about terminal elimination of **rifalazil** given in a multiple-dose regimen. Results are shown in Table 15.

TABLE 15

Pharmacokinetic Parameters in 004 Clinical Trial

Dose
Parameters 25. . .
DETD . . . four Phase I clinical trials have investigated the safety profile and pharmacokinetics in healthy male subjects following the administration of **rifalazil** as single doses (300 mg, 100 mg, 30 mg), daily doses (25 mg, 5 mg) administered for 14 days, and. . .
DETD [0201] Pharmacokinetic analysis has clearly demonstrated that the administration of food with **rifalazil** delayed absorption and increased C.sub.max and AUC in a dose-proportional manner. The mean terminal half-life seen with the 25 mg dose was about 61 hours. Accumulation of **rifalazil** with either 25 mg or 50 mg doses, given once weekly over 4 weeks to healthy subjects, appeared to be. .
.
DETD . . . which was 2 to 3 times the MIC.sub.90 of rifampin-sensitive Mycobacterium tuberculosis (15.6 ng/mL) Furthermore, because of the partitioning of **rifalazil** into macrophages, therapeutically beneficial concentrations of **rifalazil** are expected to persist in macrophages longer than in plasma. Thus, plasma concentrations that fall below the MIC.sub.90 during the. . .
DETD [0203] B. Efficacy of **Rifalazil** Treatment in TB Patients--Clinical Trial 005
DETD . . . or isoniazid combined with rifampin both administered daily, or isoniazid administered daily with either 10 mg or 25 mg of **rifalazil** administered weekly.
DETD . . . are shown in Table 18. WBC, ANC and platelet counts in patients treated with INH daily and 10/25 mg of **rifalazil** weekly, are shown in Tables 19 and 20, respectively. **Rifalazil** concentration in patients treated with INH and 10 or 25 mg of **rifalazil**, are shown in Table 21. Definite diagnosis and evaluation of treatment efficacy requires direct examination of sputum for the presence. . .
DETD . . . Group 2 received INH daily plus rifampin daily for 14 days, Group 3 received INH daily for 14 days plus **rifalazil** once per week (10 mg on day 1 and day 8) over 14 days, and Group 4 received INH daily for 14 days plus **rifalazil** once per week (25 mg on day 1 and day 8) over 14 days. Dosages of isoniazid and rifampin depended. .
.
DETD . . . received daily treatment with INH in combination with rifampin administered daily (Group 2) or INH administered daily in combination with **rifalazil** administered once-a-week at 25 mg dosages (Group 4). These data show that **rifalazil** administered weekly or twice weekly in relatively very low dosages of 10 or 25 mg is an effective substitute for. . . Sputum Baseline to Day 15 in Log.sub.10 CFU/mL
of Sputum Microbiologically Valuable Patients

	Treatment Group			
	INH	INH + RMP	INH + **Rifalazil**	INH + **Rifalazil**
Log.sub.10 CFU/mL	400 mg	400 mg + 600 mg	400 mg + 10 mg	400 mg + 25 mg
N	6 .sup.. . .			

DETD [0210] These results clearly show that administration of INH-**rifalazil** once-a-week in 10 or particularly 25 mg doses is as efficacious treatment for tuberculosis as treatment with INH-rifampin daily.
DETD . . . in all groups during the treatment but did not reach critically low levels. Once a week treatment with 10 mg **rifalazil** combined with 400 mg or less of INH administered daily did not lead to decrease in WBC.

DETD . . . drops below 1.0 K/CU MM. That level was reached in only one patient in Group 3, treated with INH plus **rifalazil** at 10 mg but that patient had a low ANC value to begin with.

DETD [0215] The important conclusions derived from the hematologic data is that **rifalazil** does not cause a greater level of hematologic disturbances (safety concerns) than rifampin which is routinely used for treatment of TB. **Rifalazil** is therefore as safe as rifampin and as efficacious in lower and less frequent dosages.

TABLE 17

WBC, ANC, and Platelet. . .

DETD [0217]

TABLE 19

WBC, ANC, and Platelet Counts (K/CU MM) - INH + 10 mg-**Rifalazil**

	Baseline	Day 4	Day 8	Day 11
WBC (K/cu mm)				
n	8	8	8	8
Mean (SD)	.sup. 7.97 (1.41)	.sup. 7.85. . .		

DETD [0218]

TABLE 20

WBC, ANC, and Platelet Counts (K/CU MM) INH + 25 mg-**Rifalazil**

	Baseline	Day 4	Day 8	Day 11
WBC (K/cu mm)				
n	7	7	7	7
Mean (SD)	.sup. 11.87 (6.27)	.sup. .sup. 10.49. . .		

DETD [0219] Table 21 summarizes the plasma concentrations data of **rifalazil** measured in patients that received **rifalazil** at zero hour. The data are separated into 2 groups and are identified as INH+10 mg **rifalazil** (Group 3) and INH+25 mg **rifalazil** (Group 4). The concentration of **rifalazil** in plasma is presented in ng/mL and are shown as a timecourse (hours and days) wherein values were determined at several times over the two weeks of the study.

TABLE 21

Rifalazil Concentration in Plasma (ng/mL)

Treatment Group	Hour 0	2	5	9	12	24	48	72

INH + 10 mg
KRM
n 4 4 4 4. . .
DETD [0220] The observed plasma levels of **rifalazil** were similar to those seen in normal volunteers. Table 21 shows that the plasma concentration of **rifalazil** increases from the zero level to 9.7 ng/mL for 10 mg of **rifalazil** and to 15.93 ng/mL in three hours showing a maximum concentration of the drug in plasma at six hours following the drug administration (12.68 ng/mL for 10 mg **rifalazil** and 28.47 ng/mL for 25 mg **rifalazil**). The drug concentration in plasma slowly decreases but there is still measurable amount of drug in plasma at 72 hours. . .
DETD [0221] The data obtained in TB patients show that **rifalazil** administered once or twice weekly is effective for treatment of tuberculosis and has lesser adverse reactions than other currently available. . .
DETD [0222] C. Comparison of **Rifalazil** Treatment with Rifampin and Rifabutin
DETD [0225] GI reactions included **heartburn**, epigastric distress, anorexia, nausea, vomiting, gas, cramps, diarrhea, sore mouth and tongue, pseudomembranous colitis, pancreatitis, and were experienced by 1%. . .
DETD [0237] **Rifalazil** has been shown to have antibacterial activity against Mycobactenium tuberculosis, Mycobacterium avium, Chlamydia pneumoniae, H. pylori and other bacteria. Despite the adverse reactions described in the clinical trials 001-004, the novel method for treatment of tuberculosis with **rifalazil** administered once or twice-a-week is a method of choice. It effectively lowers CFU in TB patients when administered in well. . .
DETD [0238] Both the animal studies and studies on human volunteers suggest that **rifalazil** has fewer side effects than rifampin, and rifabutin and has higher anti-bacterial activity, especially against Mycobacterium tuberculosis, Mycobacterium avium, Chlamydia. . .
DETD [0241] **Rifalazil** may be formulated and administered as stand-alone drug with various pharmaceutically acceptable additives and excipients, or in combination with other. . . the disease. Various combinations and ratios of drugs to each other are within the skills of the pharmacist formulating the **rifalazil** or **rifalazil** combination with other drugs.
DETD [0242] Typically, the drug product will contain **rifalazil**, mannitol, USP; hydroxypropyl cellulose, NF; colloidal silicon dioxide, NF; magnesium stearate, NF; polysorbate 80, NF; and water in proportions that permit material flow in capsule-filling equipment. For example, **rifalazil** will be prepared in No. 3 hard gelatin dark blue opaque snap fit capsules, or as tablets, injectables, suppositories, etc.
DETD [0243] For clinical studies described above, **rifalazil** capsules have been prepared at several different strengths; 5 mg, 25 mg, 50 mg, and 100 mg. The drug in. . .
DETD . . . Subjects in an open-label trial received a single or multiple dose of 5, 25, 50 or 300 mg dose of **rifalazil.** The study was a randomized, double-blind, placebo-controlled intermittent dose study designed to determine a maximum safe dosing regimen.
DETD . . . into two treatment groups, each consisting of six subjects. Subjects in each group were randomized to receive either placebo or **rifalazil** once weekly for 4 weeks with a two-week follow-up period. The two treatment groups were separated by at least two. . .
DETD [0254] Dose selection for this study was based on the safety profile of **rifalazil** obtained from three previous safety and pharmacokinetic (PK) studies. The results of these studies indicated

that the incidence of adverse. . .

DETD [0256] **Rifalazil** and matching placebo were prepared in No.3 hard gelatin dark blue opaque snap-fit capsules. **Rifalazil** capsules have been prepared at four different strengths 5 mg, 25 mg, 50 mg and 100 mg. **Rifalazil** in the 5 mg, 25 mg and 50 mg strength capsules has been blended with additional mannitol (placebo) so that. . .

DETD . . . daily, which is also typical and FDA approved TB treatment, or with 400 mg isoniazid daily and 10 mg of **rifalazil** once-a-week, or with 400 isoniazid daily and 25 mg of **rifalazil** once-a-week. Both latest regimens were experimental and performed under IND permit from FDA.

CLM What is claimed is:

1. A method for treatment of bacterial infection by once-a week or twice-a-week administration of **rifalazil** in a dosage from about 1 to about 100 mg.

2. The method of claim 1 wherein the dosage of **rifalazil** is from 5 to 50 mg administered once-a-week or twice-a-week.

3. The method of claim 2 wherein the dosage of **rifalazil** is from 10 to 25 mg administered once-a-week or twice-a-week.

6. The method of claim 5 wherein the tuberculosis is treated by once-a-week or twice-a-week administration of **rifalazil** for 4 to 62 weeks.

7. The method of claim 6 wherein additionally, the **rifalazil** is administered in combination with isoniazid, ethambutol, pyrazinamide, streptomycin, capreomycin, ethionamide, cycloserine, kanamycin, tobramycin or amikacin.

11. The method of claim 10 wherein the Chlamydia pneumoniae; infection is treated with once-a-week or twice-a-week dose of **rifalazil** in dose from 1 to about 50 mg orally.

14. The method of claim 4 wherein the **rifalazil** is administered orally, transdermally, parenterally, topically or by suppositories.

IT **129791-92-0**, Rifalazil
(rifalazil administered once- or twice-weekly for treatment of bacterial infection)

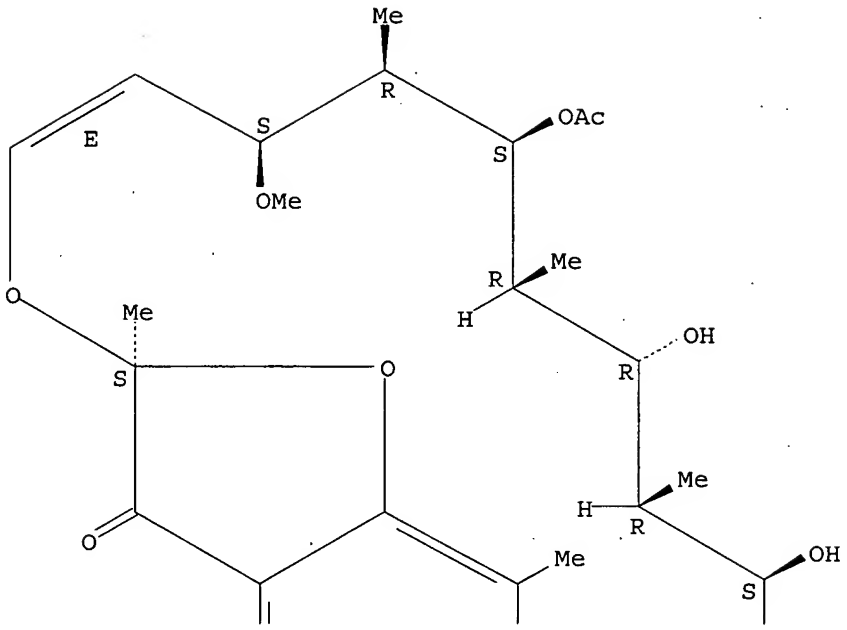
IT **129791-92-0**, Rifalazil
(rifalazil administered once- or twice-weekly for treatment of bacterial infection)

RN 129791-92-0 USPATFULL

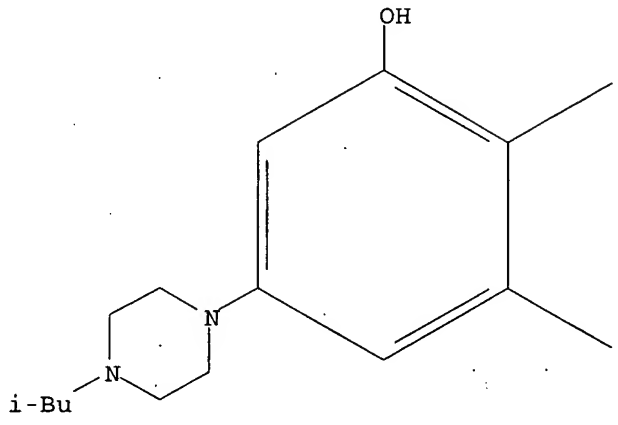
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

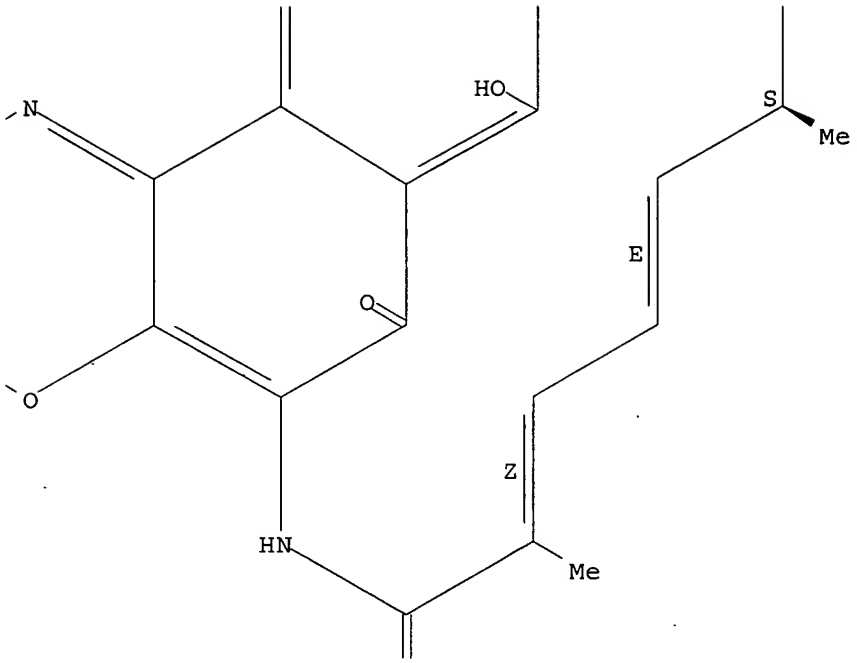
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

O

L166 ANSWER 32 OF 40 USPATFULL on STN

ACCESSION NUMBER:	2003:141106 USPATFULL
TITLE:	Lipopeptide stereoisomers, methods for preparing same, and useful intermediates
INVENTOR(S):	Morytko, Michael, Framingham, MA, UNITED STATES Zhang, Yanzhi, Sharon, MA, UNITED STATES Jung, Michael, Los Angeles, CA, UNITED STATES Finn, John, Stow, MA, UNITED STATES Bouchard, Mario, Billerica, MA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003096948	A1	20030522	
APPLICATION INFO.:	US 2002-213218	A1	20020806	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-310313P	20010806 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	CUBIST PHARMACEUTICALS, INC., 65 HAYDEN AVENUE, LEXINGTON, MA, 02421
NUMBER OF CLAIMS:	62
EXEMPLARY CLAIM:	1
LINE COUNT:	1739

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides daptomycin stereoisomeric compounds, methods and intermediates for preparing daptomycin and daptomycin stereoisomoeric compounds, as well as pharmaceutical compositions of these compounds and methods of using these compositions as antibacterial agents.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . the bacterial infection is caused by gram-positive bacteria. These organs or tissue include, without limitation, skeletal muscle, skin, bloodstream, kidneys, **heart**, lung and bone. The method of the invention may be used to treat, without limitation, skin and soft tissue infections,. . .
SUMM . . . KA 159, Dynemicin A, DX8739, DU 6681; Cefluprenam, ER 35786, Cefoselis, Sanfetrinem celexetil, HGP-31, Cefpirome, HMR-3647, RU-59863, Mersacidin, KP 736, **Rifalazil**; AM 1732, MEN 10700, Lenapenem, BO 2502A, NE-1530, PR 39, K130, OPC 20000, OPC 2045, Veneprim, PD 138312, PD 140248,. . .

L166 ANSWER 33 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2003:120756 USPATFULL
TITLE: Novel depsipeptides and process for preparing same
INVENTOR(S): Finn, John, Stow, MA, UNITED STATES
Morytko, Michael, Framingham, MA, UNITED STATES
Parr, Ian Barrie, Medford, MA, UNITED STATES
Jung, Michael, Los Angeles, CA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003083240	A1	20030501	
APPLICATION INFO.:	US 2002-213389	A1	20020806	(10)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2001-310313P	20010806	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: CUBIST PHARMACEUTICALS, INC., 65 HAYDEN AVENUE, LEXINGTON, MA, 02421
NUMBER OF CLAIMS: 30
EXEMPLARY CLAIM: 1
LINE COUNT: 2657
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to novel depsipeptide compounds. The invention also relates to pharmaceutical compositions of these compounds and methods of using these compounds as antibacterial compounds. The invention also relates to methods of producing these novel depsipeptide compounds and intermediates used in producing these compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . the bacterial infection is caused by gram-positive bacteria. These organs or tissue include, without limitation, skeletal muscle, skin, bloodstream, kidneys, **heart**, lung and bone. The method of the invention may be used to treat, without limitation, skin and soft tissue infections,. . .
SUMM . . . KA 159, Dynemicin A, DX8739, DU 6681; Cefluprenam, ER 35786, Cefoselis, Sanfetrinem celexetil, HGP-31, Cefpirome, HMR-3647, RU-59863, Mersacidin, KP 736, **Rifalazil**; AM 1732, MEN 10700, Lenapenem, BO 2502A, NE-1530, PR 39, K130, OPC 20000, OPC 2045, Veneprim, PD 138312, PD 140248,. . .

L166 ANSWER 34 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2003:65554 USPATFULL
TITLE: Methods for preparing purified lipopeptides
INVENTOR(S): Keith, Dennis, Montclair, NJ, UNITED STATES
Lai, Jan-Ji, Westborough, MA, UNITED STATES
Khalaf, Nazar, Worcester, MA, UNITED STATES
Govardhan, Chandrika, Lexington, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003045678	A1	20030306
APPLICATION INFO.:	US 2001-23517	A1	20011217 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-256268P	20001218 (60)
	US 2001-274741P	20010309 (60)
	US 2001-341315P	20011213 (60)
	US 2001-340525P	20011213 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FISH & RICHARDSON PC, 225 FRANKLIN ST, BOSTON, MA, 02110
NUMBER OF CLAIMS: 56
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 16 Drawing Page(s)
LINE COUNT: 1961
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to crystalline and crystal-like forms of lipopeptides, including daptomycin, a lipopeptide antibiotic with potent bactericidal activity against gram-positive bacteria, including strains that are resistant to conventional antibiotics. The present invention relates to methods of purifying lipopeptides, including daptomycin, a lipopeptide antibiotic with potent bactericidal activity against gram-positive bacteria, including strains that are resistant to conventional antibiotics. The present invention also relates to pharmaceutical compositions comprising the purified form of the lipopeptide and methods of using these compositions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . of any organ or tissue in the body. These organs or tissue include, without limitation, skeletal muscle, skin, bloodstream, kidneys, **heart**, lung and bone. The method of the invention may be used to treat, without limitation, skin and soft tissue infections,. . .
DETD . . . KA 159, Dynemicin A, DX8739, DU 6681; Cefluprenam, ER 35786, Cefoselis, Sanfetrinem celexetil, HGP.sub.--31, Cefpirome, HMR.sub.--3647, RU.sub.--59863, Mersacidin, KP 736, **Rifalazil**; Kosan, AM 1732, MEN 10700, Lenapenem, BO 2502A, NE.sub.--1530, PR 39, K130, OPC 20000, OPC 2045, Veneprim, PD 138312, PD. . .

L166 ANSWER 35 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2003:137076 USPATFULL
TITLE: Method for treatment of bacterial infections with once or twice-weekly administered **rifalazil**
INVENTOR(S): Rose, Lynn M., Seattle, WA, United States
Porubek, David J., Seattle, WA, United States
Montgomery, Alan B., Bellevue, WA, United States
PATENT ASSIGNEE(S): Kaneka Corporation, Osaka, JAPAN (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6566354	B1	20030520
APPLICATION INFO.:	US 2001-972320		20011005 (9)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1999-464353, filed on 15 Dec 1999, now patented, Pat. No. US 6316433		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-112921P	19981218 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Weddington, Kevin E.
LEGAL REPRESENTATIVE: Verny, Hana
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 10 Drawing Figure(s); 10 Drawing Page(s)
LINE COUNT: 1465
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for treatment of bacterial infections with **rifalazil** administered once-weekly or twice-weekly. A method for treatment of tuberculosis caused by Mycobacterium tuberculosis, infections caused by Mycobacterium avium complex, infections caused by Chlamydia pneumoniae and infections caused by Helicobacter pylori by administering to a patient suffering from the bacterial infection 1-100 mg of **rifalazil** once or twice a week. In this dose regimen, the treatment is fast, efficacious and eliminates undesirable secondary symptoms observed with daily doses of 1-50 mg of **rifalazil.**

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Method for treatment of bacterial infections with once or twice-weekly administered **rifalazil**

AB A method for treatment of bacterial infections with **rifalazil** administered once-weekly or twice-weekly. A method for treatment of tuberculosis caused by Mycobacterium tuberculosis, infections caused by Mycobacterium avium complex, . . . pneumoniae and infections caused by Helicobacter pylori by administering to a patient suffering from the bacterial infection 1-100 mg of **rifalazil** once or twice a week. In this dose regimen, the treatment is fast, efficacious and eliminates undesirable secondary symptoms observed with daily doses of 1-50 mg of **rifalazil.**

SUMM The current invention concerns a method for treatment of bacterial infections with **rifalazil** administered once-weekly or twice-weekly. In particular, the invention concerns a method for treatment of tuberculosis caused by Mycobacterium tuberculosis, infections. . . caused by Chlamydia pneumoniae and infections caused by Helicobacter pylori by administering to a patient suffering from the bacterial infection **rifalazil** once or twice a week. In this dose regimen, the treatment is fast, efficacious and eliminates undesirable secondary symptoms observed with daily doses of 1-50 mg of **rifalazil.**

SUMM . . . Chlamydia pneumoniae and H. pylori infections with once a week or twice a week administration of a relatively new antibiotic, **rifalazil**, that belongs to the class of antibiotics called ansamycins. **Rifalazil** has the same or better activity than either rifabutin or rifampin, the other two antibiotics of the same class and. . . H. pylori when administered only once a week or twice a week in doses from 1 to 50 mg. Previously, **rifalazil** has been administered on daily basis and because of the severe secondary

adverse reactions, was discontinued as a drug for. . .

SUMM **Rifalazil** compound has been described in the U.S. Pat. No. 4,983,602 where its antibacterial activity has been disclosed. Dosages described in. . . when clinical trials with these doses of the antibiotic were administered daily, many adverse reactions occurred and the treatment with **rifalazil** was discontinued.

SUMM One aspect of the current invention is a method for treatment of bacterial infections with once or twice-week administration of **rifalazil.**

SUMM Another aspect of the current invention is a method for treatment of tuberculosis with once or twice-week administration of **rifalazil** .

SUMM . . . of the current invention is a method for treatment of Mycobacterium avium complex infections with once or twice-week administration of **rifalazil.**

SUMM . . . aspect of the current invention is a method for treatment of Chlamydia pneumoniae infections with once or twice-week administration of **rifalazil.**

SUMM . . . aspect of the current invention is a method for treatment of Helicobacter pylori infections with once or twice-week administration of **rifalazil.**

DRWD . . . blood cells counts in daily dosing regimen used in a clinical trial on human volunteers where the daily dose of **rifalazil** was 5 or 25 mg compared to a control group receiving placebo.

DRWD . . . blood cells count in daily dosing regimen used in a clinical trial on human volunteers wherein the daily dose of **rifalazil** was 25 mg.

DRWD . . . blood cells count in daily dosing regimen used in a clinical trial on human volunteers wherein the daily dose of **rifalazil** was 5 mg.

DRWD . . . human volunteers where the daily dose was 5 or 25 mg compared to a control group which received placebo without **rifalazil.**

DRWD . . . in absolute neutrophil count in daily dosing regimen used in a clinical trial on human volunteers wherein daily dose of **rifalazil** was 25 mg.

DRWD . . . in absolute neutrophil count in daily dosing regimen used in a clinical trial on human volunteers wherein daily dose of **rifalazil** was 5 mg.

DRWD FIG. 7 illustrates changes in platelets counts after 20 daily administration of 5 and 25 mg **rifalazil** to healthy volunteers in a clinical trial compared to a control group receiving placebo.

DETD "**Rifalazil**" means 3'-hydroxy-5'-(4-isobutyl-1-piperazinyl)benzoxasinorifamycin also known as **KRM-1648.**

DETD "EKG" means **electrocardiogram.**

DETD . . . confirmation in vitro, in vivo and in clinical trials that once-a-week or twice-a-week doses of 1-100, preferably 1-50 mg of **rifalazil** effectively treats bacterial infection without adverse reactions and without undesirable secondary symptoms observed with daily administration of this drug.

DETD Although **rifalazil** was found to be effective against mycobacterium species, it has never been used as a therapeutic agent for treatment of mycobacterial diseases because at the daily dose regimen which was thought to be necessary to its efficacious antibacterial activity, **rifalazil** caused severe adverse reactions and secondary symptoms. The adverse reactions included flu-like symptoms with severe headache, malaise, fever, back pain, myalgia, chills, dizziness, nausea, vomiting, body pain and weakness. Additionally, the daily administration of **rifalazil** resulted in changes in blood cell counts, particularly in decrease of white blood cells counts

(leukopenia), absolute neutrophil count and platelet count as well as in decreased blood hemoglobin. For these reasons, clinical studies involving daily dosing of **rifalazil** were abandoned.

DETD It has now been found and is a subject of this invention that **rifalazil** in once-a-week or at most twice-a-week dosing regimen is effective in eradication of Mycobacterium tuberculosis, Mycobacterium avium complex, Chlamydia pneumoniae. . .

DETD **Rifalazil** and its related drugs rifampin and rifabutin, all belonging to a group collectively described as rifamycins, were known to exhibit. . .

DETD A. Physical, Chemical and Pharmaceutical Properties of **Rifalazil**

DETD **Rifalazil** is 3'-hydroxy-5'-(4-isobutyl-1-piperazinyl) benzoxasinorifamycin of the chemical structure ##STR1##

DETD **Rifalazil** is a member of the rifamycins, a complex group of antibiotics originally isolated from **Nocardia** mediterranei that exhibits antimicrobial activity against Mycobacterium spp. The rifamycins belong to a class of antibiotics called ansamycins, which contain. . .

DETD **Rifalazil** is a nonpolar molecule that is stable and essentially insoluble in water. Two chemically-related drug substances rifampin and rifabutin are. . .

DETD **Rifalazil** synthesis is disclosed in U.S. Pat. No. 4,983,602, incorporated herein by reference in its entirety. Its known in vitro and. . . Recent Res. Devel. Antimicrob. Agents Chemother., 2:37 (1997), incorporated herein by reference. While these studies confirm the antibacterial activity of **rifalazil** in vivo as well as in vitro, such activity is based on daily administration of 2.5 and 5 mg of the drug to the mice infected with M. tuberculosis, corresponding to about 175 or 350 mg **rifalazil** dose/day/70 kg human.

DETD Additionally, in vivo studies were performed where the therapeutically effective doses of **rifalazil** and rifampin were given at various intervals. When the dose 10 mg/kg (corresponding to 700 mg/70 kg human) six times. . . reduction in CFU. However, the used and documented doses were extremely and unphysioloqically high. For humans, the daily dose of **rifalazil** above 300 mg is unphysiological and even 50 mg of **rifalazil** administered to humans daily causes severe adverse reactions.

DETD **Rifalazil** was extensively tested in vitro and in vivo in animal models and compared to other ansamycins, rifampin and rifabutin. The. . .

DETD In vitro studies show that **rifalazil** acts on bacterial DNA-dependent RNA polymerase and inhibits the growth of aerobic and anaerobic gram-positive bacteria. However, **rifalazil** is relatively inactive against gram-negative bacteria. This spectrum of activity is similar to rifampin and rifabutin, two related drugs.

DETD **Rifalazil** is a potent inhibitor of many mycobacterium spp., including the M. tuberculosis (MTB) and M. avium complex (MAC), Chlamydia pneumoniae. . . depending on the degree of resistance to rifampin. When tested side by side against the same strains, the activity of **rifalazil** in vitro is consistently greater than either rifabutin or rifampin. Minimum bactericidal concentrations (MBCs) are typically 2-4 fold higher than. . .

DETD The efficacy of **rifalazil** have been examined in vivo in macrophage and in animal models. **Rifalazil** readily accumulates in human macrophages and is bactericidal at concentrations equivalent to the MBCs established in vitro. In animal models of MTB infection, **rifalazil** was the most active single-agent against organisms in the spleen and lungs, although the combination of **rifalazil** and isoniazid (INH) or **rifalazil** and pyrazinamide (PZA) was more effective against organisms in the lung than either drug alone

(Antimicrobial Agents Chemotherapy, 40: 298. . .
DETD The therapeutic effects of **rifalazil** are also long-lasting. For example, in mice infected with M. intracellulare, **rifalazil** significantly reduced the number of colony forming units (CFUs) in organs after four and eight weeks of treatment and did so to a greater extent than rifabutin or rifampin. In a rabbit model of M. avium infection, **rifalazil** also reduced the bacterial load on organs compared to controls. Treatment of MTB infection in mice with **rifalazil** and INH for 12 weeks completely sterilized the lungs and spleens of infected animals and eliminated regrowth of the organisms. . .
DETD In chronic studies with dogs and rats, the no-observed-adverse-effect-level was 1000 mg/kg. The absolute bioavailability of .sup.14C-**rifalazil** in rats at a dose of 3 mg/kg was 30 to 40%, but was reduced at higher doses. **Rifalazil** was slowly eliminated from the blood (mean terminal half-life of 12.5 hr) with a mean systemic clearance (CL/F) of 0.184. . .
DETD 2. **Rifalazil** Antibacterial Activity in Vitro
DETD The antimicrobial activity of **rifalazil** was measured in vitro against a variety of bacterial species. In vitro studies show that **rifalazil** inhibits the bacterial growth of aerobic and anaerobic gram-positive bacteria, but is relatively inactive against gram-negative bacteria. **Rifalazil** inhibits the growth of many Mycobacterium spp. (Antimicrobial Agents Chemotherapy, 35:542 (1991)), particularly the slower growing mycobacteria such as M. tuberculosis, M. avium, and M. intracellulare. Based on MIC.sub.90 comparisons, as seen in Table 1, **rifalazil** was more active than rifampin.
DETD
TABLE 1

MIC.sub.90 and Rifampin Against Mycobacterium spp
MIC.sub.90 (μg/mL)
Species No. Of Strains **Rifalazil** Rifampin

M. intracellulare 31 0.1 12.5
M. avium 18 1.56 100
M. tuberculosis 22 12.5 100
DETD The in vitro activity of **rifalazil** against M. tuberculosis has been determined by measuring the minimum inhibitory concentration (MIC) for a variety of clinical isolates and. . .
DETD
TABLE 2

Summary of In Vitro Susceptibility Studies for **Rifalazil**
MIC Range MIC.sub.90
Ref. MIC Method No. Of Strains.sup.1 (μg/mL) (μg/mL)

1 BACTEC 30 (rif.sup.r and rif.sup.s) ≤0.002 to 4.0 2.0
2 BACTEC. . .
DETD As seen in Table 2, **rifalazil** is more active than 25 rifampin based on MIC.sub.90 comparisons, however, the spectra of its antibacterial activities are similar to. . .
DETD The in vitro activity of **rifalazil** against M. tuberculosis has been determined by measuring the minimum inhibitory concentration (MIC) for a variety of clinical isolates and. . .
DETD Studies described in Antimicrobial Agents, Chemotherapy, 39: 2295, (1995) determined the MICs of **rifalazil** against thirty clinical isolates and two stock cultures (H37Rv and Kurono) of M. tuberculosis (Table 3).
DETD

TABLE 3

MIC of **Rifalazil**, Rifabutin and Rifampin
MIC (μg/mL).sup.1 for
Clinical Isolates.sup.2 Reference M.
MIC.sub.50 MIC.sub.90 tuberculosis strain
Drug 50% inhibition 90% inhibition H37Rv Kurono

Rifalazil 0.016 2.0 0.004 0.002
Rifabutin 0.063 8.0 0.016 0.016
Rifampin 4.0 >128.0 0.125 0.063

.sup.1MICs were determined by BACTEC method.
.sup.2Thirty strains were. . .

DETD Table 3 shows Minimum Inhibitory Concentrations (MICs) of **rifalazil**, rifabutin and rifampin for clinical isolates and two reference strains of Mycobacterium tuberculosis.

DETD As seen in Table 3, **rifalazil** had more than a 64-fold greater activity than rifampin and a 4-fold greater activity than rifabutin based on comparisons of the MIC.sub.50 and MIC.sub.90. This increased activity of **rifalazil** was also observed with the reference strains. An examination of the individual MICs of the thirty isolates shows that **rifalazil** was more active than rifardpin in all thirty isolates and more active than rifabutin in twenty-eight isolates.

DETD The MIC and NBC of **rifalazil** against extracellular M. tuberculosis and M. tuberculosis in human macrophages using strains H37Rv, Erdman, and Atencio were described in Antimicrobial Agents, Chemotherapy, 409:1482 (1996). Extracellular and intracellular bacteria were exposed to varying concentrations of **rifalazil** for 7 or 8 days, macrophages were lysed where applicable, then the CFUs were determined by plating on agar. The MIC was defined as the lowest concentration of **rifalazil** that inhibited more than 99% of the growth following the drug-incubation period. The MBC was defined as the lowest concentration of **rifalazil** that killed more than 99% of the bacteria following the drug-incubation period. The results of the study show that the MIC and MBC of **rifalazil** are at least 10-fold lower than rifampin for both intracellular and extracellular bacteria (Table 4).

DETD

TABLE 4

Minimum Inhibitory Concentration (MIC) and
Minimum Bactericidal Concentration (MBC) of
Rifalazil and Rifampin (RMP) Against
Mycobacterium tuberculosis Strains
Concentration (μg/mL)
Intracellulare Bacteria Extracellular Bacteria
Rifalazil Rifampin **Rifalazil** Rifampin
Strain MIC MBC MIC MBC MIC MBC MIC MBC

H37Rv 0.004 0.016 0.25 1.0 0.008 0.031 0.12 0.5
Erdman 0.008 0.008 0.12. . .

DETD 3. **Rifalazil** Antibacterial Activity In Vivo

DETD The therapeutic effect of **rifalazil** was examined by measuring gross lung lesions, bacterial loads, and survival time in mice infected with M. tuberculosis and subsequently treated with **rifalazil** or rifampin for eight weeks (Antimicrobial Agents, Chemotherapy, 39: 2295 (1995)). In each of these tests, **rifalazil** outperformed rifampin in treating the disease.

DETD The activity of **rifalazil** alone and in combination with other

drugs in mice infected with the rifampin-sensitive M. tuberculosis strain Erdman (MIC.sub.rif =0.06 kg/mL). . .

DETD Initial experiments compared the ability of **rifalazil**, rifabutin, or rifampin (all at 20 mg/kg) to reduce the bacterial load in lungs and spleens of infected mice compared to untreated mice. **Rifalazil** reduced bacterial loads to a significantly greater extent than the other two drugs (P<0.01). No significant differences were observed between. . .

DETD Additional experiments examined the ability of **rifalazil** (20 mg/kg) alone and in combination with INH (isoniazid, mg/kg), PZA (pyrazinamide, 150 mg/kg), EMB (ethambutol, 125 mg/kg), or LEV. . .

DETD . . . reduced CFUs in the spleen compared to controls, except for PZA. PZA did not significantly reduce CFUs compared to controls. **Rifalazil** was the most active single-agent against organisms in the spleen. Only the combination of **rifalazil** plus PZA was more active than **rifalazil** alone.

DETD In lungs, treatment with **rifalazil** or INH significantly reduced cell counts in lungs compared to early controls. Compared to late controls, treatment with **rifalazil**, INH, EMB, or LEV reduced cell counts in lungs. **Rifalazil** was the most active single-agent. The combinations of **rifalazil** plus INH or **rifalazil** plus PZA were more active against organisms in lungs than treatment with **rifalazil** alone.

DETD . . . 12 weeks and the regrowth of organisms in spleen and lung was measured for 24 weeks post-treatment. The combination of **rifalazil** (20 mg/kg) and INH (25 mg/kg) was significantly more effective at reducing the number of CFUs in spleens and lungs of mice compared to **rifalazil** alone (20 mg/kg), INH alone (25 mg/kg), rifampin alone (20 mg/kg), and the combination of rifampin and INH (20 mg/kg. . .

DETD **Rifalazil** activity was also tested on other bacteria and organisms. **Rifalazil** shows a strong antibacterial activity against Chlamydia pneumoniae and against Helicobacter pylori.

DETD Sensitivity testing was conducted in cell cultures against Chiamydia pneumoniae strain TW-1 83 using **rifalazil**, clanthromycin, or azithromycin. In these studies, **rifalazil** was 300-fold more potent than clanthromycin and 1500-fold more potent than erythromycin. The in vivo testing of **rifalazil** used a mouse model infected with Chlamydia pneumoniae strain AR-39. The results showed that Chlamydia pneumoniae was not detectable from the lungs of an animal five days after the cessation of **rifalazil** treatment by intraperitoneal injection of **rifalazil** at 1 mg/kg QID for three days. All control animals remained infected.

DETD **Rifalazil** bactericidal activities were also evaluated in vitro against twenty-four strains of Helicobacter pylori . In these studies, **rifalazil** exhibited more potent antimicrobial activities against Helicobacter pylori than amoxicillin and rifampin. Time-kill studies, described in Abstract, 4th Japan-Korea International. . . symposium on Microbiology, Takashimaya, Japan, Oct. 22-23 (1998), revealed that the CFUs at 24 hours in the broth medium containing **rifalazil** at 0.04 mg/mL were more than 4.5 log lower than the control at zero hours, indicating **rifalazil**'s potent bactericidal activity. Under the same conditions amoxicillin at 0.31 mg/mL produced only 1 log decrease in CFU/mL after 24. . .

DETD Results described above indicate that **rifalazil** has very good antibacterial activity and is a better choice of the drug for treatment of bacterial infections caused by. . .

DETD 5. Pharmacology of **Rifalazil**

DETD . . . studies were undertaken in mice, rats, and dogs, and in isolated guinea pig ileum. The preclinical pharmacology data showed that

rifalazil has no important central/autonomic nervous system, respiratory, **cardiovascular**, digestive system, or renal pharmacological effects.

DETD **Rifalazil** had little effect on the clinical signs or general behavior of mice following oral administration of 100, 300, or 1,000 mg/kg. **Rifalazil** had no effect on the spontaneous locomotor activity of mice at 100 and 300 mg/kg. At 1000 mg/kg, **rifalazil** caused an increase in spontaneous locomotor activity for one hour.

DETD 6. Pharmacokinetics of **Rifalazil**

DETD . . . based upon those utilized in the single and multiple-dose toxicology studies. In addition, the absorption, distribution, metabolism, and elimination of **rifalazil** was studied in rats and dogs. These studies confirmed prior findings that there are species differences vis-a-vis sensitivity to and response to treatment with **rifalazil.**

DETD Preclinical pharmacokinetic data in rats and dogs showed that the disappearance of **rifalazil** and/or metabolites from whole blood is slow and that significant whole blood concentrations can be achieved following repeated oral administration. Upon repeated dosing, a slight increase in **rifalazil** C.sub.max and AUC values was observed in rats and dogs. Such increase was consistent with the drug accumulation. Significant,metabolism of **rifalazil** through deacetylation in both dogs and rats and hydroxylation in dogs only, occurred in both single and multiple-dose studies. In addition, significant accumulation of both metabolites was observed following repeat **rifalazil** dosing in dogs.

DETD 7. Toxicology of **Rifalazil**

DETD Under the conditions of these studies, **rifalazil** was relatively well-tolerated in animal models following single or multiple-dose oral administration. Hematological changes were noted following a multiple-dose oral. . .

DETD . . . lymphocytes. Lymphoid depletion in the spleens of treated animals and decreased peripheral blood lymphocyte count show that at certain concentration, **rifalazil** causes adverse reactions. However, there was no evidence that the animals in this study were immunosuppressed, as no opportunistic infection. . .

DETD The 13-week study of daily oral administration of **rifalazil** to dogs demonstrated that the "no observable adverse effect level" was considered to be 300 mg/kg for dogs. Lower lymphocytic. . .

DETD . . . that there is clear species difference in adverse reactions response between animals and humans. While in mice, rats and dogs **rifalazil** dosages over 300 mg/kg were well tolerated in long-term studies, such tolerance was not found in human volunteers. The dose. . .

DETD A. Safety, Pharmacokinetics and Toxicity of **Rifalazil** in Healthy Volunteers

DETD A total of four clinical trials have been conducted to study the effects of **rifalazil** in humans. Two single-dose Phase 1 clinical trials (001) and (002) assessed the safety and pharmacokinetics of **rifalazil** in normal, healthy, fasted subjects. In the 001 trial, a single 300 mg dose of **rifalazil** was administered to six subjects. In the 002 trial, single doses of 30 mg or 100 mg were administered to. . .

DETD . . . (003) and fourth (004) Phase 1 clinical trials were multiple-dose studies. Because evidence from animal studies showed increased bioavailability when **rifalazil** was administered with food, the clinical trials were designed to further assess the safety and pharmacokinetics of **rifalazil** in fed, normal, healthy subjects.

DETD . . . Subjects were divided into two groups. In Group 1, eight

subjects were randomized to a daily 25 mg dose of **rifalazil** and four subjects were randomized to placebo. Numerous adverse reactions began to appear with the 25 mg dose several days. . . of 5 mg in group 2. Group 2 consisted of eight subjects randomized to a daily 5 mg dose of **rifalazil** and four subjects randomized to placebo.

DETD . . . trial (004) was a also a randomized, rising, double-blind, multiple-dose, placebo-controlled study. In this trial, weekly doses of placebo or **rifalazil** (25 mg or 50 mg) were administered to the subjects for a total of 4 weeks. All subjects received the. . . for an additional 14 days after the last dose. Four subjects were randomized to placebo, six subjects to 25 mg **rifalazil**, and eight subjects to 50 mg **rifalazil.**

DETD . . . and severity of adverse reactions, and the time to resolution. Safety was assessed by physical examination, monitoring vital signs and **cardiac** function, measurement of clinical laboratory values in blood, serum, and urine, and by documenting adverse reactions. Systemic drug levels were. . .

DETD 2. Adverse Reactions Observed After **Rifalazil** Administration to Healthy Subjects

DETD In the first (001) and second (002) clinical trials, adverse reactions, change in laboratory parameters and pharmacokinetic of **rifalazil** were observed in healthy volunteers receiving dosages of 30 mg, 100 mg and 300 mg of **rifalazil.**

DETD

TABLE 5

Adverse Reactions in Healthy Volunteers
Rifalazil Study
001 and
001 002 002
Dose
All
Body Adverse 300 mg 0 mg 30 mg 100 mg Doses
System.sup.1 Reactions n. . . 1 4
Headache 3 0 3 1 4
Malaise 1 0 0 0 1
Pain 1 0 0 0 1
CV **Tachycardia** 3 0 0 0 3
Vasodilation 0 1 1 1 3
DIG Abnormal Stools 1 0 0 0 1
Anorexia 1. . . 0 1
Sweating 1 0 0 0 1
SS Taste Prevision 1 0 0 0 1

.sup.1BODY: body as a whole; CV: **cardiovascular** system; DIG: digestive system; NER: nervous system; RES: respiratory system; SKIN: skin and appendages; SS: special senses.

DETD As seen in Table 6, 300 mg dose of **rifalazil** resulted in forty-one mild, eight moderate and four severe adverse reactions. In contrast, placebo, 30 or 100 mg doses resulted. . .

DETD . . . were decreased in a dose-dependent manner. These parameters returned to the normal range within 14 days of final administration of **rifalazil**, and were noted to be similar to effects produced by other rifamycins.

DETD The pharmacokinetics of **rifalazil** in whole blood in these two clinical trials was similar to that of **rifalazil** pharmacokinetics in plasma. Converse to data generated from animal studies, human subjects demonstrated a higher (1.6:1) plasma to blood ratio. Therefore, future pharmacokinetic analyses focused on **rifalazil** concentrations in plasma. Table 7 summarizes

noncompartmental parameters derived from plasma concentrations in fasted subjects following administration of single doses of 30 mg, 100 mg, or 300 mg of **rifalazil** in these studies.

DETD

TABLE 7

Comparison of Noncompartmental Pharmacokinetic Parameters Derived from Plasma Concentrations in Single Dose Studies 001 and 002

Trial and Dose Parameters (mean)	**Rifalazil** - 001 300 mg	**Rifalazil** - 002 100 mg	30 mg
Tmax (h)	3.0	4.0	3.1
Cmax (ng/mL)	115.7	58.6.	. .

DETD In the third (003) and fourth (004) clinical trials, adverse reactions, change in laboratory parameters and pharmacokinetics of **rifalazil** were observed.

DETD

TABLE 8

Adverse Reactions in Single-Dose and Multiple Dose Trials

Body System.sup.1	Adverse Reactions	Study **Rifalazil**-003 5 mg/day (n = 8)	**Rifalazil**-004 25 mg/day (n = 8).	**Rifalazil**-003/004 25 mg/wk .	50 mg/wk .	0 mg .	All Doses .
	Pain	2	3	0	0	0	5
	Taste Perversion	0	2	0	0	0	2

.sup.1BODY: body as a whole, CV: **cardiovascular** sytem: DIG: digestive system: MS: musculo-skeletal system, NER: nervous system, RES: respiratory system: SKIN: skin and appendages: SS: special senses

DETD

TABLE 9

Adverse Reactions Observed in 003 and 004 Clinical Trials

Adverse Reactions	Study **Rifalazil** 003 0 mg (Placebo)	5 mg/ day	25 mg/ day	All doses	**Rifalazil** 004 0 mg (Placebo).	25 mg/ .	50 mg/ .	All .

DETD . . . headache and back pain, observed in the clinical trial 003 where the drug was administered daily. When the multiple-dose of **rifalazil** 25 mg/weekly was administered, the number of adverse reactions in the same dose regimen (25 mg) decreased substantially from thirteen. . .

DETD These results clearly show that once a week dosage of **rifalazil** has much lower incidence of adverse reactions.

DETD . . . clinical trial 003 are compared to clinical trial 004, in terms of the adverse reactions associated with daily dosing of **rifalazil.** In Tables 10 and 11, the number of drug-related adverse reactions and severity of these reactions associated with daily dosing. . .

DETD As seen in Table 10, at daily dosing with 25 mg of **rifalazil**, subjects experienced total of one hundred and twelve adverse reactions while at the daily dose of 5 mg, 8 subjects. . . total of fifty-two adverse reactions. Placebo groups experienced only one adverse reaction each. This study clearly show that multiple-dosages of **rifalazil** are dose dependent and that even a relatively small dosage of 5 mg of **rifalazil** daily cause substantial increase in adverse reactions compared to placebo.

DETD . . . in Table 11, severity of the adverse reactions was also

dose-dependent. When the dosage of 25 or 5 mg of **rifalazil** was administered daily, one hundred and two and forty-six mild adverse reactions and ten and six moderate adverse reactions were. . .

DETD . . . at least one adverse reaction, compared to one of four placebo subjects. By Day 7, five subjects continued to receive **rifalazil** while three subjects dropped from the study because of adverse reactions. By Day 10, only one subject was still receiving drug. Dosing was suspended after Day 11 by the site investigator. Daily administration of **rifalazil** was, therefore, found to be unacceptable to the subjects and such daily administration had to be discontinued.

DETD . . . per patient was also about half the number in Group 2 versus Group 1. Five of the eight subjects receiving **rifalazil** completed the study. Three subjects dropped due to adverse reaction. One subject experienced half of all the recorded adverse reactions. . . adverse reactions that were graded moderate in severity within Group 2 (Table 11). Although three of the eight subjects receiving **rifalazil** reported a mild, "flu-like" symptoms, only one of these subjects discontinued the study early. All three subjects experiencing the "flu-like". . .

DETD In clinical trial 004, specifically, the adverse reactions associated with weekly dosing of **rifalazil** are listed in Tables 8 and 9, and compared to 003 trial results. Tables 12 and 13 show the number and severity of drug-related adverse reactions associated with once-a-week administration of **rifalazil** vis-a-vis each subject and each dose in 004 clinical trial.

DETD As seen in Table 12, the number of adverse reactions observed following once-a-week administration of **rifalazil** to healthy volunteers was directly related to the dosage of **rifalazil** administered. When the dosage was 25 mg/week, there were forty-six adverse reactions. When the dosage was 50 mg/week, then there. . .

DETD Details of the adverse reactions associated with weekly dosing of **rifalazil** appear in Tables 8, 9, 12 and 13. All eighteen subjects completed the 004 clinical trial. Fewer unique adverse reactions. . .

DETD . . . measurement remained within the normal established ranges. In clinical trial 003, all subjects in Group 1 receiving 25 mg of **rifalazil**/day discontinued the study early.

DETD . . . plots of white blood cell (WBC) counts of healthy volunteers receiving dosages 0 mg, 5 mg and 25 mg of **rifalazil** administered daily. Normal range of white blood cell counts, shown in the FIG. 1 as "L" and "H" lines, is. . .

DETD FIG. 2 shows individual white blood cell counts in healthy volunteers (Group 1) receiving 25 mg of **rifalazil** daily for 14 days. As seen in FIG. 2, subjects in Group 1 experienced a larger drop in WBC counts,. . .

DETD FIG. 3 shows individual white blood cell counts in healthy volunteers (Group 2) receiving 5 mg of **rifalazil** daily for 14 days. As seen in FIG. 3, subjects in Group 2 experienced lower decreases in WBC counts which. . .

DETD . . . shows mean absolute neutrophil count in twenty-four healthy volunteers following administration of 0 mg, 5 mg and 25 mg of **rifalazil** daily for 14 days. As seen in FIG. 4, the absolute neutrophil count results have shown less consistent patterns making. .

DETD FIGS. 5 and 6 show individual absolute neutrophil counts in Group 1 receiving 25 mg of **rifalazil** daily for 14 days and Group 2 receiving 5 mg **rifalazil** daily for 14 days, respectively. Four subjects in Group 1, receiving 25 mg of **rifalazil**, seen in FIG. 5, and 3 subjects in Group 2, receiving 5 mg of **rifalazil**

, seen in FIG. 6, experienced ANC values <2.0+10.sup.3/mm.sup.3, however no ANC value fell below <1.0+10.sup.3/mm.sup.3 for any individual subject.

DETD . . . in FIG. 7, demonstrated small changes relative to placebo, with fewer changes occurring in the group receiving 5 mg of **rifalazil** versus the group receiving 25 mg. All hematologic parameters returned to normal within 14 days following administration of the last. . .

DETD . . . mean white blood cell plots for once a week dosage of 0 mg (control), 25 mg and 50 mg of **rifalazil** for four weeks. The subjects' hematological parameters were followed for an additional two weeks up to day 36.

DETD When the results seen in FIG. 8 (once-a-week administration of 50 and 25 mg **rifalazil**) are compared to results seen in FIG. 1 (once-a-day administration of 5 and 25 mg of **rifalazil**), the differences in WBC counts are readily observed. In FIG. 1, both 50 and 25 dosages show continuous drop in. . .

DETD FIG. 9 shows mean absolute neutrophil counts for once-a-week dosage of 0 mg (control), 25 mg and 50 mg of **rifalazil** administered for four weeks. As above, subjects ANC were followed up to day 36. Three subjects in the 25 mg. . .

DETD FIG. 10 shows mean platelet plots for once-a-week dosage of 0 mg (control), 25 mg and 50 mg of **rifalazil** for four weeks with follow up to day 36. As seen in FIG. 10, once a week dosages of **rifalazil** on platelets were unremarkable without any observable changes outside of the normal range 150-450 K/CU MM.

DETD Pharmacokinetic analyses associated with clinical trials involved measurement of concentrations of **rifalazil** in plasma and/or whole blood of subjects participating in the four Phase 1 studies using high performance liquid chromatography. Most. . .

DETD . . . the 003 clinical trial and in Table 15 for the 004 clinical trial 004. Several pharmacokinetic patterns were consistently observed. **Rifalazil** appears to be slowly absorbed, widely distributed, and slowly eliminated via a multi-phasic process. Inter-patient variability was demonstrated.

DETD Due to extremely low levels of **rifalazil** measured in the urine, elimination of **rifalazil** seems to be non-renal, and probably occurs by the fecal route. In addition, low levels of oxidative metabolites of **rifalazil** were found in plasma. This further suggests that drug is excreted in the feces either in unchanged form or as. . .

DETD . . . 22). Because of extensive sampling after the fourth dose, this study yielded the most complete data about terminal elimination of **rifalazil** given in a multiple-dose regimen. Results are shown in Table 15.

DETD . . . four Phase I clinical trials have investigated the safety profile and pharmacokinetics in healthy male subjects following the administration of **rifalazil** as single doses (300 mg, 100 mg, 30 mg), daily doses (25 mg, 5 mg) administered for 14 days, and. . .

DETD Pharmacokinetic analysis has clearly demonstrated that the administration of food with **rifalazil** delayed absorption and increased C.sub.max and AUC in a dose-proportional manner. The mean terminal half-life seen with the 25 mg dose was about 61 hours. Accumulation of **rifalazil** with either 25 mg or 50 mg doses, given once weekly over 4 weeks to healthy subjects, appeared to be. . .

DETD . . . which was 2 to 3 times the M1C.sub.90 of rifampin-sensitive Mycobacterium tuberculosis (15.6 ng/mL) Furthermore, because of the partitioning of **rifalazil** into macrophages, therapeutically beneficial concentrations of **rifalazil** are expected to persist in macrophages longer than in plasma. Thus, plasma concentrations that

fall below the MIC.sub.90 during the. . .
DETD B. Efficacy of **Rifalazil** Treatment in TB Patients--Clinical Trial 005
DETD . . . or isoniazid combined with rifampin both administered daily, or isoniazid administered daily with either 10 mg or 25 mg of **rifalazil** administered weekly.
DETD . . . are shown in Table 18. WBC, ANC and platelet counts in patients treated with INH daily and 10/25 mg of **rifalazil** weekly, are shown in Tables 19 and 20, respectively. **Rifalazil** concentration in patients treated with INH and 10 or 25 mg of **rifalazil**, are shown in Table 21. Definite diagnosis and evaluation of treatment efficacy requires direct examination of sputum for the presence. . .
DETD . . . Group 2 received INH daily plus rifampin daily for 14 days, Group 3 received INH daily for 14 days plus **rifalazil** once per week (10 mg on day 1 and day 8) over 14 days, and Group 4 received INH daily for 14 days plus **rifalazil** once per week (25 mg on day 1 and day 8) over 14 days. Dosages of isoniazid and rifampin depended. . .
DETD . . . received daily treatment with INH in combination with rifampin administered daily (Group 2) or INH administered daily in combination with **rifalazil** administered once-a-week at 25 mg dosages (Group 4). These data show that **rifalazil** administered weekly or twice weekly in relatively very low dosages of 10 or 25 mg is an effective substitute for. . .
DETD . . . Sputum Baseline to Day 15 in Log.sub.10 CFU/mL of Sputum Microbiologically Valuable Patients

Treatment Group	INH + RMP	INH + **Rifalazil**	
INH 400 mg +	400 mg +	INH + **Rifalazil**	
Log.sub.10 CFU/mL	400 mg	600 mg	10 mg 400 mg + 25 mg
N	6	4	6 6
Mean (SD)	-1.58 (0.51)	-2.61. . .	

DETD These results clearly show that administration of INH-**rifalazil** once-a-week in 10 or particularly 25 mg doses is as efficacious treatment for tuberculosis as treatment with INH-rifampin daily.
DETD . . . in all groups during the treatment but did not reach critically low levels. Once a week treatment with 10 mg **rifalazil** combined with 400 mg or less of INH administered daily did not lead to decrease in WBC.
DETD . . . drops below 1.0 K/CU MM. That level was reached in only one patient in Group 3, treated with INH plus **rifalazil** at 10 mg but that patient had a low ANC value to begin with.
DETD The important conclusions derived from the hematologic data is that **rifalazil** does not cause a greater level of hematologic disturbances (safety concerns) than rifampin which is routinely used for treatment of TB. **Rifalazil** is therefore as safe as rifampin and as efficacious in lower and less frequent dosages.
DETD
TABLE 19

WBC, ANC, and Platelet Counts (K/CU MM) - INH + 10 mg-**Rifalazil**

	Baseline	Day 4	Day 8	Day 11	Day 15	Day 28	Day 42
WBC (K/cu mm)							
n	8	8	8	8. . .			

DETD
TABLE 20

WBC, ANC, and Platelet Counts (K/CU MM)
INH + 25 mg-**Rifalazil**
Baseline Day 4 Day 8 Day 11 Day 15 Day 28 Day 42

WBC
(K/cu mm)
n 7 7 7 7. . .

DETD Table 21 summarizes the plasma concentrations data of **rifalazil** measured in patients that received **rifalazil** at zero hour. The data are separated into 2 groups and are identified as INH+10 mg **rifalazil** (Group 3) and INH+25 mg **rifalazil** (Group 4). The concentration of **rifalazil** in plasma is presented in ng/mL and are shown as a timecourse (hours and days) wherein values were determined at. . .

DETD
TABLE 21

Rifalazil Concentration in Plasma (ng/mL)
Hour
Day 8 Day 8
Transparent Group 0 3 6 9 12 24 48 72 M-0. . .

DETD The observed plasma levels of **rifalazil** were similar to those seen in normal volunteers. Table 21 shows that the plasma concentration of **rifalazil** increases from the zero level to 9.7 ng/mL for 10 mg of **rifalazil** and to 15.93 ng/mL in three hours showing a maximum concentration of the drug in plasma at six hours following the drug administration (12.68 ng/mL for 10 mg **rifalazil** and 28.47 ng/mL for 25 mg **rifalazil**). The drug concentration in plasma slowly decreases but there is still measurable amount of drug in plasma at 72 hours. . .

DETD The data obtained in TB patients show that **rifalazil** administered once or twice weekly is effective for treatment of tuberculosis and has lesser adverse reactions than other currently available. . .

DETD C. Comparison of **Rifalazil** Treatment with Rifampin and Rifabutin

DETD GI reactions included **heartburn**, epigastric distress, anorexia, nausea, vomiting, gas, cramps, diarrhea, sore mouth and tongue, pseudomembranous colitis, pancreatitis, and were experienced by 1%. . .

DETD **Rifalazil** has been shown to have antibacterial activity against Mycobacterium tuberculosis, Mycobacterium avium, Chlamydia pneumoniae, H. pylori and other bacteria. Despite the adverse reactions described in the clinical trials 001-004, the novel method for treatment of tuberculosis with **rifalazil** administered once or twice-a-week is a method of choice. It effectively lowers CFU in TB patients when administered in well. . .

DETD Both the animal studies and studies on human volunteers suggest that **rifalazil** has fewer side effects than rifampin, and rifabutin and has higher anti-bacterial activity, especially against Mycobacterium tuberculosis, Mycobacterium avium, Chlamydia. . .

DETD **Rifalazil** may be formulated and administered as stand-alone drug with various pharmaceutically acceptable additives and excipients, or in combination with other. . . the disease. Various combinations and ratios of drugs to each other are within the skills of the pharmacist formulating the **rifalazil** or **rifalazil** combination with other drugs.

DETD Typically, the drug product will contain **rifalazil**, mannitol, USP; hydroxypropyl cellulose, NF; colloidal silicon dioxide, NF; magnesium stearate, NF; polysorbate 80, NF; and water in proportions that permit material flow in capsule-filling equipment. For example, **rifalazil** will be prepared in No. 3 hard gelatin dark blue opaque snap fit capsules, or as tablets, injectables, suppositories, etc.

DETD For clinical studies described above, **rifalazil** capsules have been prepared at several different strengths; 5 mg, 25 mg, 50 mg, and 100 mg. The drug in. . .

DETD Subjects in an open-label trial received a single or multiple dose of 5, 25, 50 or 300 mg dose of **rifalazil.** The study was a randomized, double-blind, placebo-controlled intermittent dose study designed to determine a maximum safe dosing regimen.

DETD . . . into two treatment groups, each consisting of six subjects. Subjects in each group were randomized to receive either placebo or **rifalazil** once weekly for 4 weeks with a two-week follow-up period. The two treatment groups were separated by at least two. . .

DETD Dose selection for this study was based on the safety profile of **rifalazil** obtained from three previous safety and pharmacokinetic (PK) studies. The results of these studies indicated that the incidence of adverse. . .

DETD **Rifalazil** and matching placebo were prepared in No. 3 hard gelatin dark blue opaque snap-fit capsules. **Rifalazil** capsules have been prepared at four different strengths 5 mg, 25 mg, 50 mg and 100 mg. **Rifalazil** in the 5 mg, 25 mg and 50 mg strength capsules has been blended with additional mannitol (placebo) so that. . .

DETD . . . daily, which is also typical and FDA approved TB treatment, or with 400 mg isoniazid daily and 10 mg of **rifalazil** once-a-week, or with 400 isoniazid daily and 25 mg of **rifalazil** once-a-week. Both latest regimens were experimental and performed under IND permit from FDA.

CLM What is claimed is:

1. A method for treating a bacterial infection in a human, said method comprising once-a-week or twice-a-week administration of **rifalazil** in a dosage of 1 to 100 mg.

2. The method of claim 1, wherein the dosage of **rifalazil** is 5 to 50 mg.

3. The method of claim 2, wherein the dosage of **rifalazil** is 10 to 25 mg.

4. The method of claim 1, wherein said **rifalazil** is administered for 4 to 52 weeks.

6. The method of claim 1 wherein the **rifalazil** is administered orally, transdermally, parenterally, topically, by inhalation, or by suppositories.

8. The method of claim 6 wherein the **rifalazil** is administered orally.

9. A method for treating a bacterial infection in a human, said method comprising once-a-week or twice-a-week administration of **rifalazil** in a dosage of 25-50 mg/week.

11. A method for treating a tuberculosis patient, said method comprising administering to said patient isoniazid daily and **rifalazil**

once-a-week or twice-a-week.

. . . treatment of bacterial infection in a human, comprising: a) a pharmaceutical composition comprising an active ingredient consisting of 25-50 mg **rifalazil** and a pharmaceutically acceptable excipient; and b) instructions directing a user to administer the pharmaceutical composition once-a-week or twice-a-week.

IT **129791-92-0**, Rifalazil
(rifalazil administered once- or twice-weekly for treatment of bacterial infection)

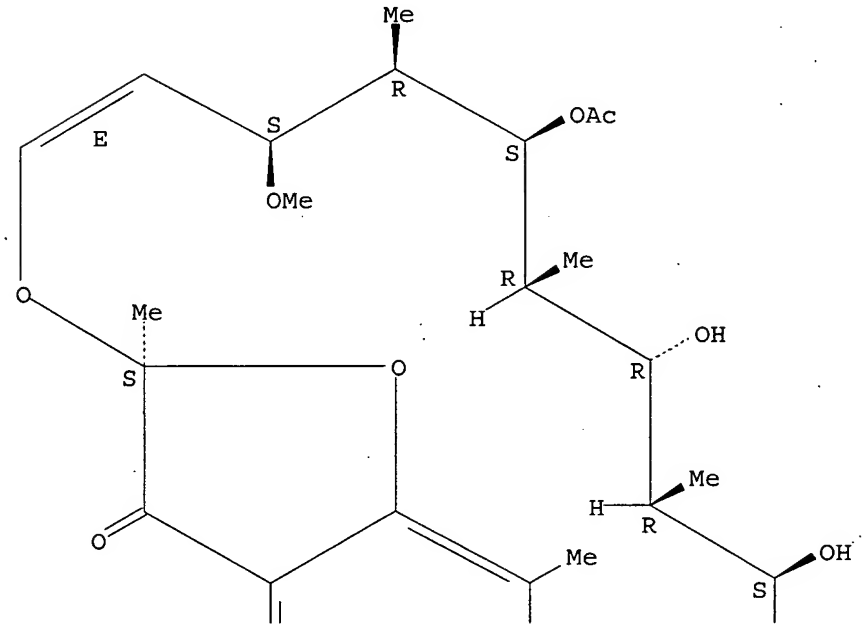
IT **129791-92-0**, Rifalazil
(rifalazil administered once- or twice-weekly for treatment of bacterial infection)

RN 129791-92-0 USPATFULL

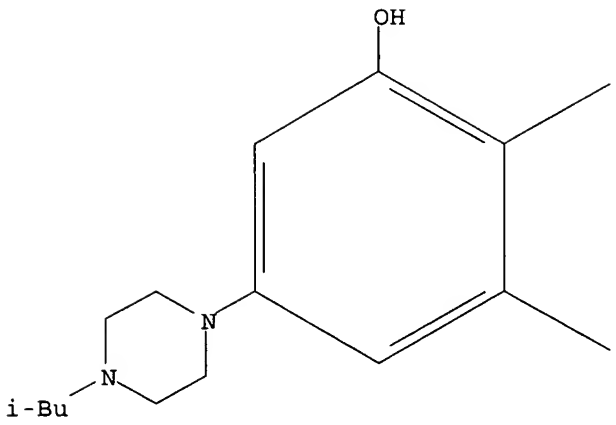
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

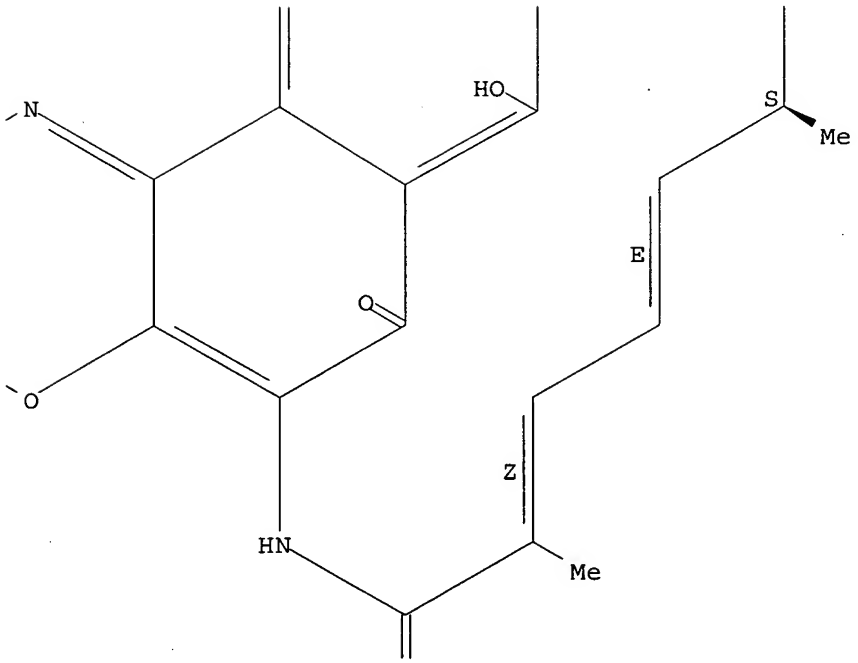
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

O

L166 ANSWER 36 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2002:235511 USPATFULL
TITLE: Methods for improved diagnosis and treatment of mycobacterial infections

INVENTOR(S): Zhang, Ying, Ellicott City, MD, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002127700	A1	20020912	
	US 6664096	B2	20031216	
APPLICATION INFO.:	US 2001-5920	A1	20011207	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-251785P	20001208 (60)
	US 2001-294602P	20010601 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Whitham, Curtis & Christofferson, PC, Suite 305, 11491 Sunset Hills Road, Reston, VA, 20190
NUMBER OF CLAIMS: 64
EXEMPLARY CLAIM: 1
LINE COUNT: 1590
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Media for growth enhancement and resuscitation of mycobacteria (such as Mycobacterium tuberculosis, Mycobacterium paratuberculosis, and Mycobacterium leprae) are provided. The media comprise isolated cell extract, early-stationary-phase or stationary phase supernatant, or a substantially purified component thereof such as a protein, a peptide fragment of the protein, or a phospholipid. The protein is Rv1147c and the phospholipid or a component of a phospholipid. Diagnostic methods and kits utilizing the media are also provided, as well as treatment methods utilizing spent culture supernatant and cell extracts, or components thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . in 7H9 medium followed by plating at different dilutions on 7H11 agar plates containing 4 μg/ml phosphatidylserine (derived from bovine **brain**, containing a mixture of two unknown fatty acyl groups, Sigma Chemical Co.) or phosphatidylserine dioleoyl. The plates were incubated at. . .

DETD . . . (A, B, and C) derived from mice that had been treated with antituberculosis drugs isoniazid and a new rifamycin derivative **rifalazil** did not give CFU on mycobacterial 7H11 agar plates. A resuscitation experiment was set up as follows to determine if. . .

L166 ANSWER 37 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2002:113039 USPATFULL
TITLE: Novel lipopeptides as antibacterial agents
INVENTOR(S): Hill, Jason, Auburndale, MA, UNITED STATES
Parr, Ian, Medford, MA, UNITED STATES
Morytko, Michael, Framingham, MA, UNITED STATES
Siedlecki, Jim, Burlington, MA, UNITED STATES
Yang Yu, Xiang, Billerica, MA, UNITED STATES
Silverman, Jared, Brookline, MA, UNITED STATES
Keith, Dennis, Arlington, MA, UNITED STATES
Finn, John, Stow, MA, UNITED STATES
Christensen, Dale, Apex, NC, UNITED STATES
Lazarova, Tsvetelina, Brookline, MA, UNITED STATES
Watson, Alan D., Lexington, MA, UNITED STATES
Zhang, Yan, Sharon, MA, UNITED STATES

	NUMBER	KIND	DATE

PATENT INFORMATION: US 2002058785 A1 20020516
US 6794490 B2 20040921
APPLICATION INFO.: US 2000-739535 A1 20001215 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-170945P	19991215 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FISH & NEAVE, 1251 AVENUE OF THE AMERICAS, 50TH FLOOR, NEW YORK, NY, 10020-1105
NUMBER OF CLAIMS: 25
EXEMPLARY CLAIM: 1
LINE COUNT: 1731
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel lipopeptide compounds. The invention also relates to pharmaceutical compositions of these compounds and methods of using these compounds as antibacterial compounds. The invention also relates to methods of producing these novel lipopeptide compounds and intermediates used in producing these compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . the bacterial infection is caused by gram-positive bacteria. These organs or tissue include, without limitation, skeletal muscle, skin, bloodstream, kidneys, **heart**, lung and bone. The method of the invention may be used to treat, without limitation, skin and soft tissue infections,. . .

DETD . . . 159, Dynemicin A, DX8739, DU 6681; Ceftuprenam, ER 35786, Cefoselis, Sanfetrinem celexetil, HGP-3 1, Cefpirome, HMR-3647, RU-59863, Mersacidin, KP 736, **Rifalazil**; Kosan, AM 1732, MEN 10700, Lenapenem, BO 2502A, NE-1530, PR 39, K130, OPC 20000, OPC 2045, Veneprim, PD 138312, PD. . .

CLM What is claimed is:

. . . KA 159, Dynemicin A, DX8739, DU 6681; Ceftuprenam, ER 35786, Cefoselis, Sanfetrinem celexetil, HGP-31, Cefpirome, HMR-3647, RU-59863, Mersacidin, KP 736, **Rifalazil**; Kosan, AM 1732, MEN 10700, Lenapenem, BO 2502A, NE-1530, PR 39, K130, OPC 20000, OPC 2045, Veneprim, PD 138312, PD. . .

IT 54-85-3, Isoniazid 56-75-7, Chloramphenicol 58-14-0, Pyrimethamine 61-32-5, Methicillin 61-33-6, biological studies 65-49-6, Paraaminosalicylic acid 68-41-7, Cycloserine 74-55-5, Ethambutol 98-96-4, Pyrazinamide 104-06-3, Thiacetazone 154-21-2, Lincomycin 303-81-1, Novobiocin 443-48-1, Metronidazole 536-33-4, Ethionamide 587-23-5, Methenamine mandelate 738-70-5, Trimethoprim 751-94-0, Fusidate sodium 1403-66-3, Gentamicin 1404-90-6, Vancomycin 1405-87-4, Bacitracin 1405-97-6, Gramicidin 1695-77-8, Spectinomycin 5714-73-8, Methenamine hippurate 11003-38-6, Capreomycin 12650-69-0, Mupirocin 14222-60-7, Prothionamide 15318-45-3, Thiamphenicol 18323-44-9, Clindamycin 23155-02-4, Fosfomycin 32988-50-4, Viomycin 37517-28-5, Amikacin 56391-56-1, Netilmicin 61036-62-2, Teicoplanin 64221-86-9, Imipenem 65243-33-6 73090-70-7, Epiroprim 73384-59-5, Ceftriaxone 78110-38-0, Aztreonam 84957-29-9, Cefpirome 87238-52-6 87638-04-8, Carumonam 109545-84-8, Ziracin 111452-88-1 113359-04-9, Cefozopran 116853-25-9, Ceftuprenam 120410-24-4, Biapenem 120788-07-0, Sulopenem 122841-10-5, Cefoselis 124412-57-3, Dynemicin A 126602-89-9, Synercid 128104-18-7, Mersacidin **129791-92-0** , Rifalazil 129951-17-3, DU 6681 133686-28-9, KP 736 138126-04-2, BO 2502A 139637-11-9, PR 39 141611-76-9, Sanfetrinem sodium 141646-08-4, Sanfetrinem-cilexetil 143158-16-1, PD 138312 143383-20-4 145260-69-1, CP 111905 147214-63-9, Cyclothialidine 149137-72-4

149951-16-6, Lenapenem 157542-49-9, CS-834 158295-97-7 161856-02-6, OCA-983 165800-03-3, Linezolid 171099-57-3, LY333328 176950-36-0, Micacocidin A 186319-97-1, ER 35786 191114-48-4, HMR3647 195874-55-6, MEN 10700 205925-96-8 252188-71-9 345631-66-5, Eveminomycin 345631-69-8, CL 331022 345631-70-1, KA 159 345631-86-9, GV 143253 345631-92-7, A 99058.1 345631-93-8, A 165600 345631-94-9, A 179796 345631-96-1, HGP 31 345631-97-2, RU 59863 345631-98-3, Kosan 345631-99-4, AM 1732 345632-00-0, NE 153O 345632-01-1, OPC 20000 345632-02-2, OPC 2045 345632-44-2, Veneprim 345632-48-6, SEP 132613 345632-67-9, SB 275833 345632-68-0 345632-69-1, SUN-A 0026 345632-74-8, T 3811
(preparation of novel lipopeptides as antibacterial agents)

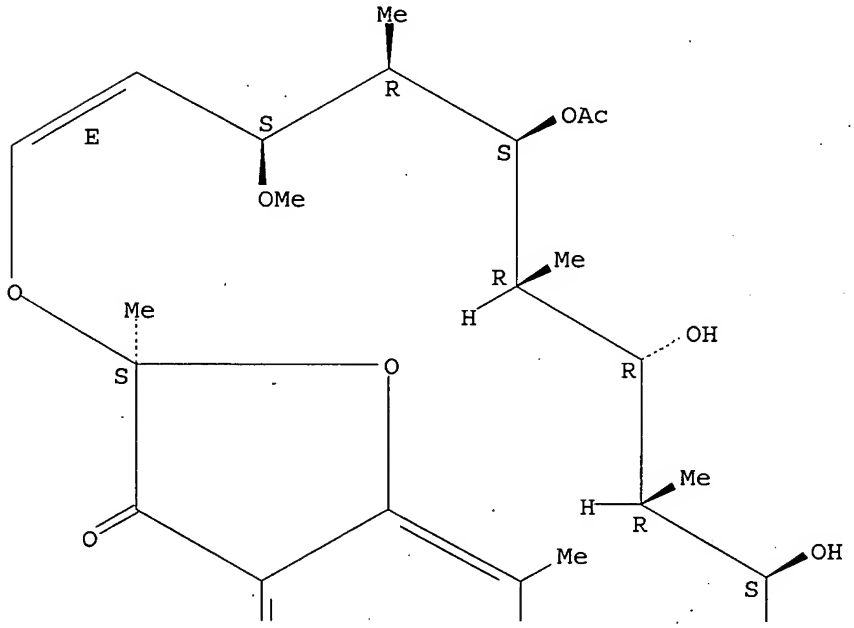
IT **129791-92-0**, Rifalazil
(preparation of novel lipopeptides as antibacterial agents)

RN 129791-92-0 USPATFULL

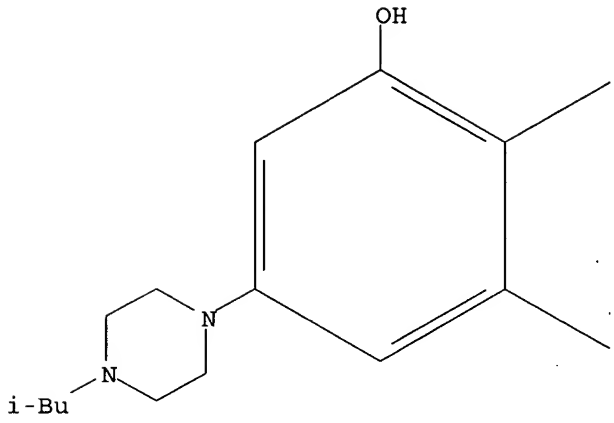
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

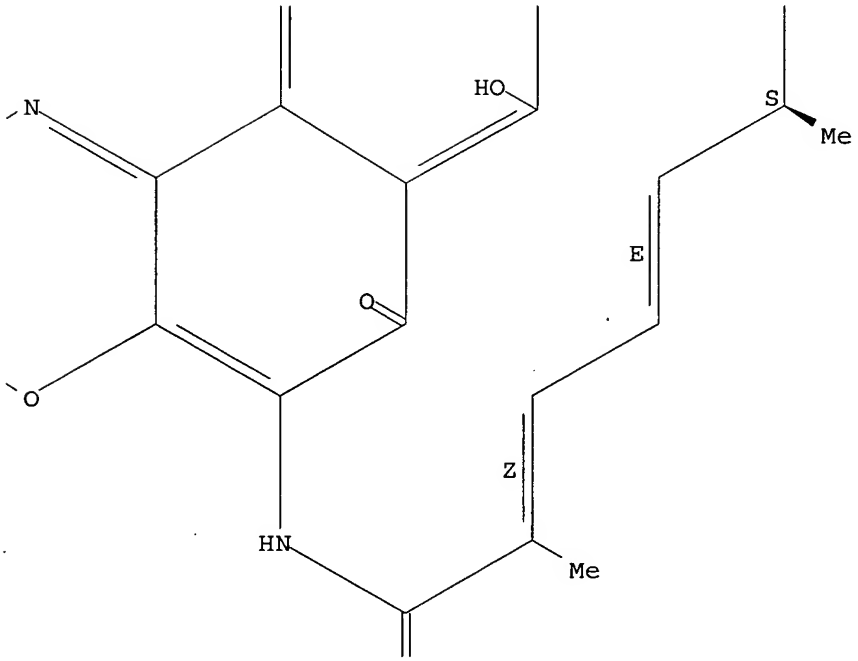
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

O

L166 ANSWER 38 OF 40 USPATFULL on STN
ACCESSION NUMBER: 2002:43557 USPATFULL
TITLE: Novel lipopeptides as antibacterial agents
INVENTOR(S): Hill, Jason, Auburndale, MA, UNITED STATES

Parr, Ian, Medford, MA, UNITED STATES
Morytko, Michael, Framingham, MS, UNITED STATES
Siedlecki, Jim, Burlington, MA, UNITED STATES
Yang Yu, Xiang, Billerica, MA, UNITED STATES
Silverman, Jared, Brookline, MA, UNITED STATES
Keith, Dennis, Arlington, MA, UNITED STATES
Finn, John, Stow, MA, UNITED STATES
Christensen, Dale, Apex, NC, UNITED STATES
Lazarova, Tsvetelina, Brookline, MA, UNITED STATES
Watson, Alan D., Lexington, MA, UNITED STATES
Zhang, Yan, Sharon, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002025924	A1	20020228
	US 6911525	B2	20050628
APPLICATION INFO.:	US 2000-738742	A1	20001215 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-170943P	19991215 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FISH & NEAVE, 1251 AVENUE OF THE AMERICAS, 50TH FLOOR, NEW YORK, NY, 10020-1105
NUMBER OF CLAIMS: 30
EXEMPLARY CLAIM: 1
LINE COUNT: 2492

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel lipopeptide compounds. The invention also relates to pharmaceutical compositions of these compounds and methods of using these compounds as antibacterial compounds. The invention also relates to methods of producing these novel lipopeptide compounds and intermediates used in producing these compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . the bacterial infection is caused by gram-positive bacteria. These organs or tissue include, without limitation, skeletal muscle, skin, bloodstream, kidneys, **heart**, lung and bone. The method of the invention may be used to treat, without limitation, skin and soft tissue infections, . . .

SUMM . . . KA 159, Dynemicin A, DX.sup.8739, DU 6681; -Ceftuprenam, ER 35786, -Cefoselis, Sanfetrinem celexetil, HGP31, -Cefpirome, HMR.sup.3647, RU59863, Mersacidin, KP 736, **Rifalazil**; Kosan, AM 1732, MEN 10700, Lenapenem, BO 2502A, NE1530, PR 39, K130, OPC 20000, OPC 2045, Veneprim, PD 138312, PD. . .

CLM What is claimed is:

. . . KA 159, Dynemicin A, DX-8739, DU 6681; -Ceftuprenam, ER 35786, -Cefoselis, Sanfetrinem celexetil, HGP-31, -Cefpirome, HMR-3647, RU-59863, Mersacidin, KP 736, **Rifalazil**; Kosan, AM 1732, MEN 10700, Lenapenem, BO 2502A, NE-1530, PR 39, K130, OPC 20000, OPC 2045, Veneprim, PD 138312, PD. . .

IT 54-85-3, Isoniazid 56-75-7, Chloramphenicol 58-14-0, Pyrimethamine 61-32-5, Methicillin 61-33-6, biological studies 65-49-6, Paraaminosalicylic acid 68-41-7, Cycloserine 74-55-5, Ethambutol 98-96-4, Pyrazinamide 104-06-3, Thiacetazone 154-21-2, Lincomycin 303-81-1, Novobiocin 443-48-1, Metronidazole 536-33-4, Ethionamide 587-23-5, Methenamine mandelate 738-70-5, Trimethoprim 751-94-0, Fusidate sodium 1403-66-3, Gentamicin 1404-90-6, Vancomycin 1405-87-4, Bacitracin 1405-97-6, Gramicidin 1695-77-8, Spectinomycin

5714-73-8, Methenamine hippurate 11003-38-6, Capreomycin 12650-69-0, Mupirocin 14222-60-7, Prothionamide 15318-45-3, Thiamphenicol 18323-44-9, Clindamycin 23155-02-4, Fosfomycin 32988-50-4, Viomycin 37517-28-5, Amikacin 56391-56-1, Netilmicin 61036-62-2, Teicoplanin 64221-86-9, Imipenem 65243-33-6 73090-70-7, Epiroprim 73384-59-5, Ceftriaxone 78110-38-0, Aztreonam 84957-29-9, Cefpirome 87638-04-8, Carumonam 99376-22-4, Ritipenem acoxyl 109545-84-8, Ziracin 111452-88-1 113359-04-9, Cefozopran 116853-25-9, Cefluprenam 120410-24-4, Biapenem 120788-07-0, Sulopenem 122841-10-5, Cefoselis 124412-57-3, Dynemicin A 126602-89-9, Synercid 128104-18-7, Mersacidin **129791-92-0**, Rifalazil 129951-17-3, DU 6681 133686-28-9, KP 736 138126-04-2, BO 2502A 139637-11-9, PR 39 141611-76-9, Sanfetrinem sodium 141646-08-4, Sanfetrinem-cilexetil 143158-16-1, PD 138312 143383-20-4 145260-69-1, CP 111905 147214-63-9, Cyclothialidine 149137-72-4 149951-16-6, Lenapenem 157542-49-9, CS-834 158295-97-7, TOC 39 161856-02-6, OCA-983 165800-03-3, Linezolid 171099-57-3, LY333328 176950-36-0, Micacocidin A 186319-97-1, ER 35786 191114-48-4, HMR3647 195874-55-6, MEN 10700 205925-96-8, Sch 40832 252188-71-9, Ro 65-5788 345631-66-5, Eveminomycin 345631-69-8, CL 331022 345631-70-1, KA 159 345631-86-9, GV 143253 345631-92-7, A 99058.1 345631-93-8, A 165600 345631-94-9, A 179796 345631-96-1, HGP 31 345631-97-2, RU 59863 345631-98-3, Kosan 345631-99-4, AM 1732 345632-00-0, NE 1530 345632-01-1, OPC 20000 345632-02-2, OPC 2045 345632-44-2, Veneprim 345632-48-6, SEP 132613 345632-67-9, SB 275833 345632-68-0 345632-69-1, SUN-A 0026 345632-74-8, T 3811
(preparation of novel lipopeptides as antibacterial agents)

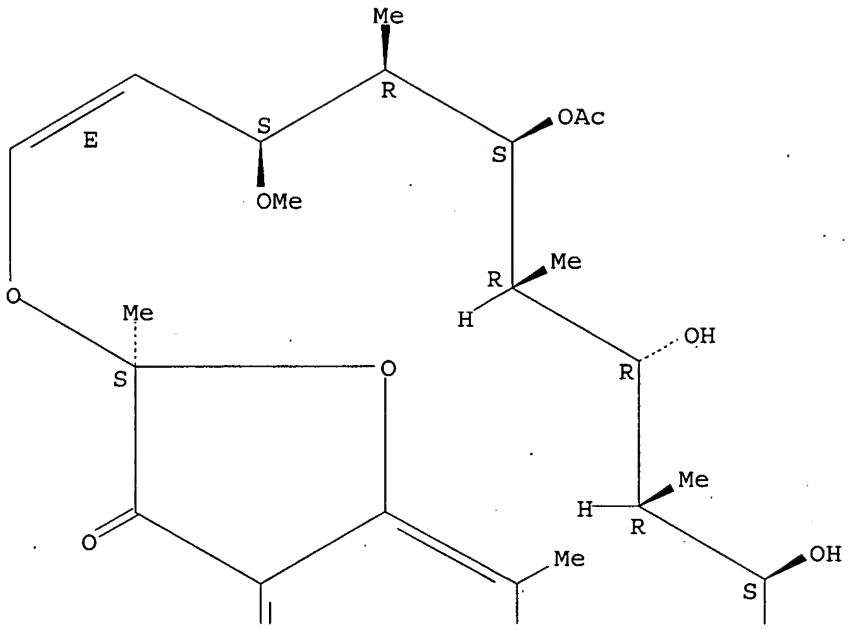
IT **129791-92-0**, Rifalazil
(preparation of novel lipopeptides as antibacterial agents)

RN 129791-92-0 USPATFULL

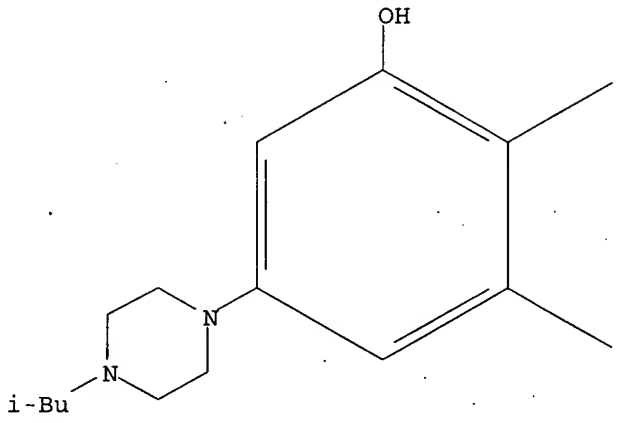
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

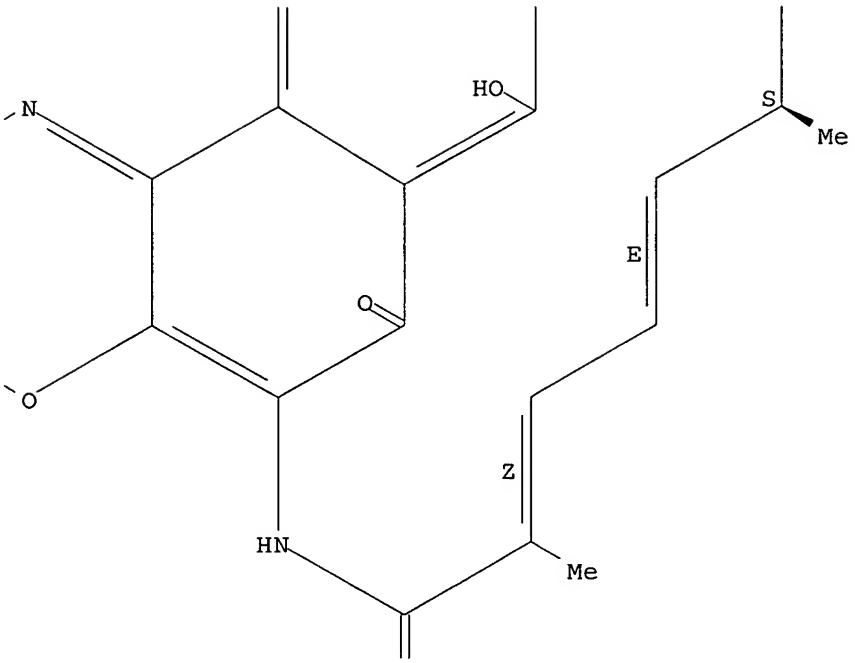
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

O

L166 ANSWER 39 OF 40 USPATFULL on STN

ACCESSION NUMBER:	2002:310939 USPATFULL
TITLE:	Use of rifamycin derivative for treating mastitis in a domestic animal
INVENTOR(S):	Fujii, Kenji, Akashi, JAPAN Yamashita, Katsuji, Kobe, JAPAN Hosoe, Kazunori, Takasago, JAPAN Yancey, Jr., Robert J., Salem, CT, United States Watts, Jeffrey L., Portage, MI, United States
PATENT ASSIGNEE(S):	Kaneka Corporation, Osaka, JAPAN (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6486161	B1	20021126	
	WO 9906047		19990211	
APPLICATION INFO.:	US 2000-463580		20000523	(9)
	WO 1998-US15308		19980729	
			20000523	PCT 371 date

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Fay, Zohreh
LEGAL REPRESENTATIVE:	Armstrong, Westerman & Hattori, LLP
NUMBER OF CLAIMS:	3
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	0 Drawing Figure(s); 0 Drawing Page(s)

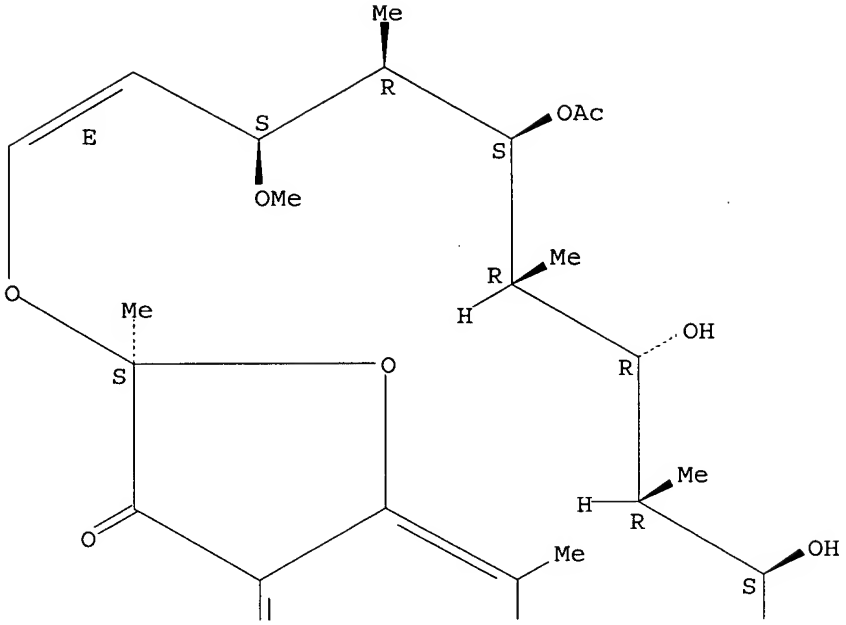
LINE COUNT: 522
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for treating mastitis in a domestic animal in need of such a treatment, which comprises administering to the animal a pharmaceutical composition comprising a rifamycin derivative of the formula (1):
##STR1##

wherein R is an alkyl group having 1 to 7 carbon atoms or a physiologically acceptable salt thereof as an active ingredient, and a physiologically acceptable carrier. The present invention provides a novel therapeutic method effective for treatment of mastitis caused by bacterial infection in a domestic animal.

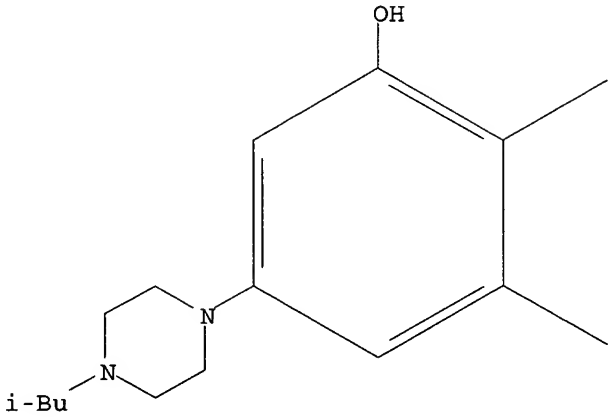
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . of 1 ml of water to each well. The number of viable bacteria was then estimated by plate counts on **brain heart** infusion agar. The criteria for intracellular killing by a rifamycin derivative were that the bacteria count must be significantly reduced. . .
DETD . . . a rifampin-resistant isolate: S. aureus 6097, a strain used in the mouse mastitis test and originally from a case of **gangrenous** bovine mastitis; S. aureus B83-1, derived from the Newbould 305 strain; and S. aureus ATCC 29213, the in vitro control. . .
IT 6998-60-3D, Rifamycin, derivs. 13292-46-1, Rifampin 105396-59-6 **129791-92-0** 133633-12-2 143526-65-2 143526-66-3
(rifamycin derivative for treating mastitis in a domestic animal)
IT **129791-92-0**
(rifamycin derivative for treating mastitis in a domestic animal)
RN 129791-92-0 USPATFULL
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

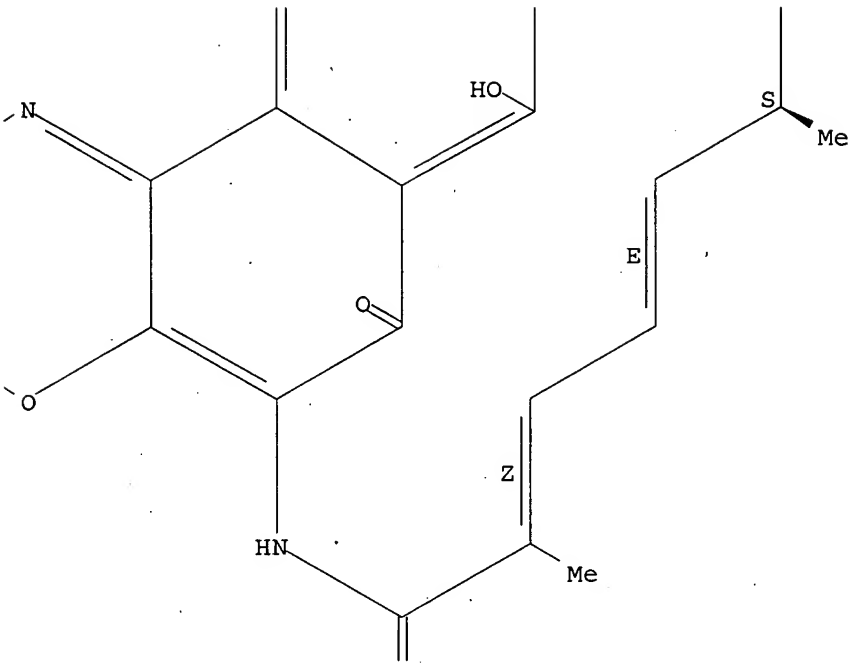
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

L166 ANSWER 40 OF 40 USPATFULL on STN

ACCESSION NUMBER:	2001:202616 USPATFULL
TITLE:	Method for treatment of bacterial infections with once or twice-weekly administered **rifalazil**
INVENTOR(S):	Rose, Lynn M., Seattle, WA, United States Porubek, David J., Seattle, WA, United States Montgomery, Alan B., Bellevue, WA, United States
PATENT ASSIGNEE(S):	Kaneka Corporation, Osaka, Japan (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6316433	B1	20011113	
APPLICATION INFO.:	US 1999-464353		19991215	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1998-112921P	19981218	(60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Weddington, Kevin E.
LEGAL REPRESENTATIVE:	Verny, Hana
NUMBER OF CLAIMS:	16
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	10 Drawing Figure(s); 10 Drawing Page(s)
LINE COUNT:	1673

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for treatment of bacterial infections with **rifalazil** administered once-weekly or twice-weekly. A method for treatment of tuberculosis caused by Mycobacterium tuberculosis, infections caused by Mycobacterium avium complex, infections caused by Chlamydia pneumoniae and infections caused by Helicobacter pylori by administering to a patient suffering from the bacterial infection 1-100 mg of **rifalazil** once or twice a week. In this dose regimen, the treatment is fast, efficacious and eliminates undesirable secondary symptoms observed with daily doses of 1-50 mg of **rifalazil.**

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Method for treatment of bacterial infections with once or twice-weekly administered **rifalazil**
AB A method for treatment of bacterial infections with **rifalazil** administered once-weekly or twice-weekly. A method for treatment of tuberculosis caused by Mycobacterium tuberculosis, infections caused by Mycobacterium avium complex,. . . pneumoniae and infections caused by Helicobacter pylori by administering to a patient suffering from the bacterial infection 1-100 mg of **rifalazil** once or twice a week. In this dose regimen, the treatment is fast, efficacious and eliminates undesirable secondary symptoms observed with daily doses of 1-50 mg of **rifalazil.**
SUMM The current invention concerns a method for treatment of bacterial infections with **rifalazil** administered once-weekly or twice-weekly. In particular, the invention concerns a method for treatment of tuberculosis caused by Mycobacterium tuberculosis, infections. . . caused by Chlamydia pneumoniae and infections caused by Helicobacter pylori by administering to a patient suffering from the bacterial infection **rifalazil** once or twice a week. In this dose regimen, the treatment is fast, efficacious and eliminates undesirable secondary symptoms observed with daily doses of 1-50 mg of **rifalazil.**
SUMM . . . Chlamydia pneumoniae and H. pylori infections with once a week or twice a week administration of a relatively new antibiotic, **rifalazil**, that belongs to the class of antibiotics called ansamycins. **Rifalazil** has the same or better activity than either rifabutin or rifampin, the other two antibiotics of the same class and. . . H. pylori when administered only once a week or twice a week in doses from 1 to 50 mg. Previously, **rifalazil** has been administered on daily basis and because of the severe secondary adverse reactions, was discontinued as a drug for. . .
SUMM **Rifalazil** compound has been described in the U.S. Pat. No. 4,983,602 where its antibacterial activity has been disclosed. Dosages described in. . . when clinical trials with these doses of the antibiotic were administered daily, many adverse reactions occurred and the treatment with **rifalazil** was discontinued.
SUMM One aspect of the current invention is a method for treatment of bacterial infections with once or twice-week administration of **rifalazil.**
SUMM Another aspect of the current invention is a method for treatment of tuberculosis with once or twice-week: administration of **rifalazil.**
SUMM . . . of the current invention is a method for treatment of Mycobacterium avium complex infections with once or twice-week administration of **rifalazil.**
SUMM . . . aspect of the current invention is a method for treatment of Chlamydia pneumoniae infections with once or twice-week administration of **rifalazil.**
SUMM . . . aspect of the current invention is a method for treatment of

Helicobacter pylori infections with once or twice-week administration of **rifalazil.**

DRWD . . . blood cells counts in daily dosing regimen used in a clinical trial on human volunteers where the daily dose of **rifalazil** was 5 or 25 mg compared to a control group receiving placebo.

DRWD . . . blood cells count in daily dosing regimen used in a clinical trial on human volunteers wherein the daily dose of **rifalazil** was 25 mg.

DRWD . . . blood cells count in daily dosing regimen used in a clinical trial on human volunteers wherein the daily dose of **rifalazil** was 5 mg.

DRWD . . . human volunteers where the daily dose was 5 or 25 mg compared to a control group which received placebo without **rifalazil.**

DRWD . . . in absolute neutrophil count in daily dosing regimen used in a clinical trial on human volunteers wherein daily dose of **rifalazil** was 25 mg.

DRWD . . . in absolute neutrophil count in daily dosing regimen used in a clinical trial on, human volunteers wherein daily dose of **rifalazil** was 5 mg.

DRWD FIG. 7 illustrates changes in platelets counts after 20 daily administration of 5 and 25 mg **rifalazil** to healthy volunteers in a clinical trial compared to a control group receiving placebo.

DETD "**Rifalazil**" means 3'-hydroxy-5'-(4-isobutyl-1-piperazinyl)benzoxasinorifamycin also known as **KRM-1648.**

DETD "EKG" means **electrocardiogram.**

DETD . . . confirmation in vitro, in vivo and in clinical trials that: once-a-week or twice-a-week doses of 1-100, preferably 1-50 mg of **rifalazil** effectively treats bacterial infection without adverse reactions and without undesirable secondary symptoms observed with daily administration of this drug.

DETD Although **rifalazil** was found to be effective against mycobacterium species, it has never been used as a therapeutic agent for treatment of mycobacterial diseases because at the daily dose regimen which was thought to be necessary to its efficacious antibacterial activity, **rifalazil** caused severe adverse reactions and secondary symptoms. The adverse reactions included flu-like symptoms with severe headache, malaise, fever, back pain, myalgia, chills, dizziness, nausea, vomiting, body pain and weakness. Additionally, the daily administration of **rifalazil** resulted in changes in blood cell counts, particularly in decrease of white blood cells counts (leukopenia), absolute neutrophil count and platelet count as well as in decreased blood hemoglobin. For these reasons, clinical studies involving daily dosing of **rifalazil** were abandoned.

DETD It has now been found and is a subject of this invention that **rifalazil** in once-a-week or at most twice-a-week dosing regimen is effective in eradication of Mycobacterium tuberculosis, Mycobacterium avium complex, Chlamydia pneumoniae. . .

DETD **Rifalazil** and its related drugs rifampin and rifabutin, all belonging to a group collectively described as rifamycins, were known to exhibit. . .

DETD A. Physical, Chemical and Pharmaceutical Properties of **Rifalazil**

DETD **Rifalazil** is 3'-hydroxy-5'-(4-isobutyl-1-piperazinyl) benzoxasinorifamycin of the chemical structure ##STR1##

DETD **Rifalazil** is a member of the rifamycins, a complex group of antibiotics originally isolated from **Nocardia** mediterranei that exhibits antimicrobial activity against Mycobacteriun spp. The rifamycins belong to a class of antibiotics called. ansamycins, which contain. . .

DETD **Rifalazil** is a nonpolar molecule that is stable and

essentially insoluble in water. Two chemically-related drug substances rifampin and rifabutin are. . .

DETD **Rifalazil** synthesis is disclosed in U.S. Pat. No. 4,983,602, incorporated herein by reference in its entirety. Its known in vitro and. . . Recent Res. Devel. Antimicrob. Agents Chemother., 2:37 (1997), aincorporated herein by reference. While these studies confirm the antibacterial activity of **rifalazil** in vivo as well as in vitro, such activity is based on daily administration of 2.5 and 5 mg of the drug to the mice infected with M. tuberculosis, corresponding to about 175 or 350 mg **rifalazil** dose/day/70 kg human.

DETD Additionally, in vivo studies were performed where the therapeutically effective doses of **rifalazil** and rifampin were given at various intervals. When the dose 10 mg/kg (corresponding to 700 mg/70 kg human) six times. . . reduction in CFU. However, the used and documented doses were extremely and unphysioloqically high. For humans, the daily dose of **rifalazil** above 300 mg is unphysiological and even 50 mg of **rifalazil** administered to humans daily causes severe adverse reactions.

DETD **Rifalazil** was extensively tested in vitro and in vivo in animal models and compared to other ansamycins, rifampin and rifabutin. The. . .

DETD In vitro studies show that **rifalazil** acts on bacterial DNA-dependent RNA polymerase and inhibits the growth of aerobic and anaerobic gram-positive bacteria. However, **rifalazil** is relatively inactive against gram-negativet bacteria. This spectrum of activity is similar to rifampin and rifabutin, two related drugs.

DETD **Rifalazil** is a potent inhibitor of many mycobacteriun Spp., including the M. tuberculosis (MTB) and M. avium complex (MAC), Chlamydia pneumoniae. . . depending on the degree of resistance to rifampin. When tested side by side against the same strains, the activity of **rifalazil** in vitro is consistently greater than either rifabutin or rifampin. Minimum bactericidal concentrations (MBCs) are typically 2-4 fold higher than. . .

DETD The efficacy of **rifalazil** have been examined in vivo in macrophage and in animal models. **Rifalazil** readily accumulates in human macrophages and is bactericidal at concentrations equivalent to the MBCs established in vitro. In animal models of MTB infection, **rifalazil** was the most active single-agent against organisms in the spleen and lungs, although the combination of **rifalazil** and isoniazid (INH) or **rifalazil** and pyrazinamide (PZA) was more effective against organisms in the lung than either drug alone (Antimicrobial Agents Chemotherapy, 40: 298. . .

DETD The therapeutic effects of **rifalazil** are also long-lasting. For example, in mice infected with M. intracellulare, **rifalazil** significantly reduced the number of colony forming units (CFUs) in organs after four and eight. weeks of treatment and did so to a greater extent than rifabutin or rifampin. In a rabbit model of M. avium infection, **rifalazil** also reduced the bacterial load on organs compared to controls. Treatment of MTB infection in mice with **rifalazil** and INH for 12 weeks completely sterilized the lungs and spleens of infected animals and eliminated regrowth of the organisms. . .

DETD In chronic studies with dogs and rats, the no-observed-adverse-effect-level was 1000 mg/kg. The absolute bioavailability of .sup.14 C-**rifalazil** in rats at a dose of 3 mg/kg was 30 to 40%, but was reduced at higher doses. **Rifalazil** was slowly eliminated from the blood (mean terminal half-life of 12.5 hr) with a mean systemic clearance (CL/F) of 0.184. . .

DETD 2. **Rifalazil** Antibacterial Activity in Vitro

DETD The antimicrobial activity of **rifalazil** was measured in vitro

against a variety of bacterial species. In vitro studies show that **rifalazil** inhibits the bacterial growth of aerobic and anaerobic gram-positive bacteria, but is relatively inactive against gram-negative bacteria. **Rifalazil** inhibits the growth of many Mycobacterium spp. (Antimicrobial Agents Chemotherapy, 35:542 (1991)), particularly the slower growing mycobacteria such as M. tuberculosis, M. avium, and M. intracellulare. Based on MIC.sub.90 comparisons, as seen in Table 1, **rifalazil** was more active than rifampin.

DETD TABLE 1

MIC.sub.90 and Rifampin Against Mycobacterium spp

Species	No. of Strains	MIC.sub.90 (μg/mL) **Rifalazil**	Rifampin
M. intracellulare	31	0.1	12.5
M. avium	18	1.56	100
M. tuberculosis	22	12.5	100

* MIC determined by agar. . .

DETD The in vitro activity of **rifalazil** against M. tuberculosis has been determined by measuring the minimum inhibitory concentration (MIC) for a variety of clinical isolates and. . .

DETD TABLE 2

Summary of In Vitro Susceptibility Studies for **Rifalazil**

Ref.	MIC Method	No. Of Strains	MIC Range .sup.1 (μg/mL)	MIC.sub.90 (μg/mL)
1	BACTEC	30 (rif.sup.r and rif.sup.s)	≤0.002 to 4.0	2.0
2	BACTEC. . .			

DETD As seen in Table 2, **rifalazil** is more active than 25rifampin based on MIC.sub.90 comparisons, however, the spectra of its antibacterial activities are similar to rifampin.

DETD The in vitro activity of **rifalazil** against M. tuberculosis has been determined by measuring the minimumi inhibitory concentration (MIC) for a variety of clinical isolates and. . .

DETD Studies described in Antimicrobial Agents, Chemotherapy, 39: 2295, (1995) determined the MICs of **rifalazil** against thirty clinical isolates and two stock cultures (H37Rv and Kurono) of M. tuberculosis (Table 3).

DETD TABLE 3

MIC of **Rifalazil**, Rifabutin and Rifampin

Drug	MIC (μg/mL) .sup.1 for Clinical Isolates .sup.2 MIC50 50% inhibition	MIC90 90% inhibition	Reference M. tuberculosis strain H37Rv	Kurono
Rifalazil	0.016	2.0	0.004	0.002
Rifabutin	0.063	8.0	0.016	0.016
Rifampin	4.0	>128.0	0.125	0.063

.sup.1 MICs were determined by BACTEC method.

.sup.2 Thirty strains. . .

DETD Table 3 shows Minimum Inhibitory Concentrations (MICS) of **rifalazil**, rifabutin and rifampin for clinical isolates and two reference strains of Mycobacterium tuberculosis.

DETD As seen in Table 3, **rifalazil** had more than a 64-fold greater activity than rifampin and a 4-fold greater, activity than rifabutin based on comparisons of the MIC.sub.50 and MIC.sub.90. This increased activity of **rifalazil** was also observed with the reference strains. An examination of the individual MICs of the thirty isolates shows that **rifalazil** was more active than rifampin in all thirty isolates and more active than rifabutin in twenty-eight isolates.

DETD The MIC and NBC of **rifalazil** against extracellular M. tuberculosis and M. tuberculosis in human macrophages using strains H37Rv, Erdman, and Atencio were described in Antimicrobial Agents, Chemotherapy, 409:1482 (1996). Extracellular and intracellular bacteria

were exposed to varying concentrations of **rifalazil** for 7 or 8 days, macrophages were lysed where applicable, then the CFUs werea determined by plating on agar. The MIC was defined as the 16 lowest concentration of **rifalazil** that inhibited more than 99% of the growth following the drug-incubation period. The MBC was defined as the lowest concentration of **rifalazil** that killed more than 99% of the bacteria following the drug-incubation period. The results of the study show that the MIC and MBC of **rifalazil** are at least 10-fold lower than rifampin for both intracellular and extracellular bacteria (Table 4).

DETD TABLE 4

Minimum Inhibitory Concentration (MIC) and
Minimum Bactericidal Concentration (MBC) of
Rifalazil and Rifampin (RMP) Against
Mycobacterium tuberculosis Strains

	Concentration (μg/mL)							
	Intracellulare Bacteria				Extracellular Bacteria			
	Rifalazil		Rifampin		**Rifalazil**		Rifampin	
Strain	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
H37Rv	0.004	0.016	0.25	1.0	0.008	0.031	0.12	0.5
Erdman	0.008	0.008	0.12.	.	.			

DETD 3. **Rifalazil** Antibacterial Activity In Vivo

DETD The therapeutic effect of **rifalazil** was examined by measuring gross lung lesions, bacterial loads, and survival time in mice infected with M. tuberculosis and subsequently treated with **rifalazil** or rifampin for eight weeks (Antimicrobial Agents, Chemotherapy, 39: 2295 (1995)). In each of these tests, **rifalazil** outperformed rifampin in treating the disease.

DETD The activity of **rifalazil** alone and in combination with other drugs in mice infected with the rifampin-sensitive M. tuberculosis strain Erdman (MIC.sub.rif =0.06 kg/mL). . . .

DETD Initial experiments compared the ability of **rifalazil**, rifabutin, or rifampin (all at 20 mg/kg) to reduce the bacterial load in lungs and spleens of infected mice compared to untreated mice. **Rifalazil** reduced bacterial loads to a significantly greater extent than the other two drugs ($P<0.01$). No significant differences were observed between. . .

DETD Additional experiments examined the ability of **rifalazil** (20 mg/kg) alone and in combination with INH (isoniazid, mg/kg), PZA (pyrazinamide, 150 mg/kg), EMB (ethambutol, 125 mg/kg), or LEV. . .

DETD . . . reduced CFUs irn the spleen compared to controls, except for PZA. PZA did not significantly reduce CFUs compared to controls. **Rifalazil** was the most active single-agent against organisms in the spleen. Only the combination of **rifalazil** plus PZA was more active than **rifalazil** alone.

DETD In lungs, treatment with **rifalazil** or INH significantly reduced cell counts in lungs compared to early controls. Compared to late controls, treatment with **rifalazil**, INH, EMB, or LEV reduced cell counts in lungs. **Rifalazil** was the most active single-agent. The combinations of **rifalazil** plus INH or **rifalazil** plus PZA were more active against organisms in lungs than treatment with **rifalazil** alone.

DETD . . . 12 weeks and the regrowth of organisms in spleen and lung was measured for 24 weeks post-treatment. The combination of **rifalazil** (20 mg/kg) and INH (25 mg/kg) was significantly more effective at reducing the number of CFUs in spleens and lungs of mice compared to **rifalazil** alone (20 mg/kg), INH alone (25 mg/kg), rifampin alone (20 mg/kg), and the combination of rifampin and INH (20 mg/kg. . .

DETD **Rifalazil** activity was also tested on other bacteria and

organisms. **Rifalazil** shows a strong antibacterial activity against Chlamydia pneumoniae and against Helicobacter pylori.

DETD Sensitivity testing was conducted in cell cultures3 against Chlamydia pneumoniae strain TW-1 83 using **rifalazil**, clanthromycin, or azithromycin. In these studies, **rifalazil** was 300-fold more potent than clanthromycin and 1500-fold more potent than erythromycin. The in vivo testing of **rifalazil** used a mouse model infected with Chlamydia pneumoniae strain AR-39. The results showed that Chlamydia pneumoniae was not detectable from the lungs of an animal five days after the cessation of **rifalazil** treatment by intraperitoneal injection of **rifalazil** at 1 mg/kg QID for three days. All control animals remained infected.

DETD **Rifalazil** bactericidal activities were also evaluated in vitro against twenty-four strains of Helicobacter pylori. In these studies, **rifalazil** exhibited more potent antimicrobial activities against Helicobacter pylori than amoxicillin and rifampin. Time-kill studies, described in Abstract, 4th Japan-Korea International. . . Symposium on Microbiology, Takashimaya, Japan, Oct. 22-23 (1998), revealed that the CFUs at 24 hours in the broth medium containing **rifalazil** at 0.04 mg/mL were more than 4.5 log lower than the control at zero hours, indicating **rifalazil**'s potent bactericidal activity. Under the same conditions amoxicillin at 0.31 mg/mL produced only 1 log decrease in CFU/mL after 24. . .

DETD Results described above indicate that **rifalazil** has ver-y good antibacterial activity and is a better choice of the drug for treatment of bacterial infections caused by. . .

DETD 5. Pharmacology of **Rifalazil**

DETD . . . studies were undertaken in mice, rats, and dogs, and in isolated guinea pig ileum. The preclinical pharmacology data showed that **rifalazil** has no important central/autonomic nervous system, respiratory, **cardiovascular**, digestive system, or renal pharmacological effects.

DETD **Rifalazil** had little effect on the clinical signs or general behavior of mice following oral administration of 100, 300, or 1,000 mg/kg. **Rifalazil** had no effect on the spontaneous locomotor activity of mice at 100 and 300 mg/kg. At 1000 mg/kg, **rifalazil** caused an increase in spontaneous locomotor activity for one hour.

DETD 6. Pharmacokinetics of **Rifalazil**

DETD . . . based upon those utilized in the single and multiple-dose toxicology studies. In addition, the absorption, distribution, metabolism, and elimination of **rifalazil** was studied in rats and dogs. These studies confirmed prior findings that there are species differences vis-a-vis sensitivity to and response to treatment with **rifalazil.**

DETD Preclinical pharmacokinetic data in rats and dogs showed that the disappearance of **rifalazil** and/or metabolites from whole blood is slow and that significant whole blood concentrations can be achieved following repeated oral administration. Upon repeated dosing, a slight increase in **rifalazil** C:sub.max and AUC values was observed in rats and dogs. Such increase was consistent with the drug accumulation. Significant metabolism of **rifalazil** through deacetylation in both dogs and rats and hydroxylation in dogs only, occurred in both single and multiple-dose studies. In addition, significant accumulation of both metabolites was observed following repeat **rifalazil** dosing in dogs.

DETD 7. Toxicology of **Rifalazil**

DETD Under the conditions of these studies, **rifalazil** was relatively well-tolerated in animal models following single or multiple-dose oral administration. Hematological changes were noted following a multiple-dose oral. . .

DETD . . . lymphocytes. Lymphoid depletion in the spleens of treated animals and decreased peripheral blood lymphocyte count show that at certain concentration, **rifalazil** causes adverse reactions. However, there was no evidence that the animals in this study were immunosuppressed, as no opportunistic infection. . .

DETD The 13-week study of daily oral administration of **rifalazil** to dogs demonstrated that the "no observable adverse effect level" was considered to be 300 mg/kg for dogs. Lower lymphocytic. . .

DETD . . . that there is clear species difference in adverse reactions response between animals and humans. While in mice, rats, and dogs **rifalazil** dosages over 300 mg/kg were well tolerated in long-term studies, such tolerance was not found in human volunteers. The dose. . .

DETD A. Safety, Pharmacokinetics and Toxicity of **Rifalazil** in Healthy Volunteers

DETD A total of four clinical trials have been conducted to study the effects of **rifalazil** in humans. Two single-dose Phase 1 clinical trials (001) and (002) assessed the safety and pharmacokinetics of **rifalazil** in normal, healthy, fasted subjects. In the 001 trial, a single 300 mg dose of **rifalazil** was administered to six subjects. In the 002 trial, single doses of 30 mg or 100 mg were administered to. . .

DETD . . . (003) and fourth (004) Phase 1 clinical trials were multiple-dose studies. Because evidence from animal studies showed increased bioavailability when **rifalazil** was administered with food, the clinical trials were designed to further assess the safety and pharmacokinetics of **rifalazil** in fed, normal, healthy subjects.

DETD . . . Subjects were divided into two groups. In Group 1, eight subjects were randomized to a daily 25 mg dose oif **rifalazil** and four subjects were randomized to placebo. Numerous adverse reactions began to appear with the 25 mg dose several days. . . of 5 mg in group 2. Group 2 consisted of eight subjects randomized to a daily 5 mg dose of **rifalazil** and four subjects randomized to placebo.

DETD . . . trial (004) was a also a randomized, rising, double-blind, multiple-dose, placebo-controlled study. In this trial, weekly doses of placebo or **rifalazil** (25 mg or 50 mg) were administered to the subjects for a total of 4 weeks. All subjects received the. . . for an additional 14 days after the last dose. Four subjects were randomized to placebo, six subjects to 25 mg **rifalazil**, and eight subjects to 50 mg **rifalazil.**

DETD . . . and severity of adverse reactions, and the time to resolution. Safety was assessed by physical examination, monitoring vital signs and **cardiac** function, measurement of clinical laboratory values in blood, serum, and urine, and by documenting adverse reactions. Systemic drug levels were. . .

DETD 2. Adverse Reactions Observed After **Rifalazil** Administration to Healthy Subjects

DETD In the first (001) and second (002) clinical trials, adverse reactions, change in laboratory parameters and pharmacokinetic of **rifalazil** were observed in healthy volunteers receiving dosages of 30 mg, 100 mg and 300 mg of **rifalazil.**

DETD TABLE 5

Adverse Reactions in Healthy Volunteers

		Rifalazil Study				
		001	002			001 and 002
		Dose				
Body	Adverse	300 mg	0 mg	30 mg	100 mg	All Doses

System.sup.1 Reactions n. . . 1 4
Headache 3 0 3 1 4
Malaise 1 0 0 0 1
Pain 1 0 0 0 1
CV **Tachycardia** 3 0 0 0 3
Vasodilation 0 1 1 1 3
DIG Abnormal Stools 1 0 0 0 1
Anorexia 1. . . 1
Sweating 1 0 0 0 1
SS Taste Prevision 1 0 0 0 1
.sup.1 BODY: body as a whole; CV: **cardiovascular** system; DIG: digestive system; NER: nervous system; RES: respiratory system; SKIN: skin and appendages; SS: special senses.

DETD As seen in Table 6, 300 mg dose of **rifalazil** resulted in forty-one mild, eight moderate and four severe adverse reactions. In contrast, placebo, 30 or 100 mg doses resulted. . .

DETD . . . were decreased in a dose-dependent manner. These parameters returned to the normal range within 14 days of final administration of **rifalazil**, and were noted to be similar to effects produced by other rifamycins.

DETD The pharmacokinetics of **rifalazil** in whole blood in these two clinical trials was similar to that of **rifalazil** pharmacokinetics in plasma. Converse to data generated from animal studies, human subjects demonstrated a higher (1.6:1) plasma to blood ratio. Therefore, future pharmacokinetic analyses focused on **rifalazil** concentrations in plasma. Table 7 summarizes noncompartmental parameters derived from plasma concentrations in fasted subjects following administration of single doses of 30 mg, 100 mg, or 300 mg of **rifalazil** in these studies.

DETD TABLE 7

Comparison of Noncompartmental Pharmacokinetic Parameters Derived from Plasma Concentrations in Single Dose Studies 001 and 002

	Trial and Dose		
Parameters (mean)	**Rifalazil** - 001 300 mg	**Rifalazil** - 002 100 mg	30 mg
Tmax (h)	3.0	4.0	3.1
Cmax (ng/mL)	115.7	58.6	17.8
Half-life. . .			

DETD In the third (003) and fourth (004) clinical trials, adverse reactions, change in laboratory parameters and pharmacokinetics of **rifalazil** were observed.

DETD TABLE 8

Adverse Reactions in Single-Dose and Multiple Dose Trials

		Study					
		Rifalazil-003		**Rifalazil**-004			
	Rifalazil-003/004						
Body System.sup.1	Adverse Reactions	5 mg/day (n = 8)	25 mg/day (n = 8). . .	25 mg/wk Pain	50 mg/wk 2	0 mg 0	All Doses 3
		0	0	5			
	Taste Perversion	0	2	0	0	0	2

BODY: body as a whole; CV: **cardiovascular** system; DIG: digestive system; MS: musculo-skeletal system; NER: nervous system; RES: respiratory system; SKIN: skin and appendages; SS: special senses.

DETD TABLE 9

Adverse Reactions Observed in 003 and 004 Clinical Trials

	Study					
	Rifalazil 003			**Rifalazil** 004		
Adverse	0 mg	5 mg	25 mg	0 mg	25 mg	50 mg

Reactions (Placebo) /day /day All doses (Placebo) /wk. . .
DETD . . . headache and back pain, observed in the clinical trial 003 where the drug was administered daily. When the multiple-dose of **rifalazil** 25 mg/weekly was administered, the number of adverse reactions in the same dose regimen (25 mg) decreased substantially from thirteen. . .
DETD These results clearly show that once a week dosage of **rifalazil** has much lower incidence of adverse reactions.
DETD . . . clinical trial 003 are compared to clinical trial 004, in terms of the adverse reactions associated with daily dosing of **rifalazil.** In Tables 10 and 11, the number of drug-related adverse reactions and severity of these reactions associated with daily dosing. . .
DETD As seen in Table 10, at daily dosing with 25 mg of **rifalazil**, subjects experienced total of one hundred and twelve adverse reactions while at the daily dose of 5 mg, 8 subjects. . . total of fifty-two adverse reactions. Placebo groups experienced only one adverse reaction each. This study clearly show that multiple-dosages of **rifalazil** are dose dependent and that even a relatively small dosage of 5 mg of **rifalazil** daily cause substantial increase in adverse reactions compared to placebo.
DETD . . . in Table 11, severity of the adverse reactions was also dose-dependent. When the dosage of 25 or 5 mg of **rifalazil** was administered daily, one hundred and two and forty-six mild adverse reactions and ten and six moderate adverse reactions were. . .
DETD . . . at least one adverse reaction, compared to one of four placebo subjects. By Day 7, five subjects continued to receive **rifalazil** while three subjects dropped from the study because of adverse reactions. By Day 10, only one subject was still receiving drug. Dosing was suspended after Day 11 by the site investigator. Daily administration of **rifalazil** was, therefore, found to be unacceptable to the subjects and such daily administration had, to be discontinued.
DETD . . . per patient was also about half the number in Group 2 versus Group 1. Five of the eight subjects receiving **rifalazil** completed the study. Three subjects dropped due to adverse reaction. One subject experienced half of all the recorded adverse reactions. . . adverse reactions that were graded moderate in severity within Group 2 (Table 11). Although three of the eight subjects receiving **rifalazil** reported a mild, "flu-like" symptoms, only one of these subjects discontinued the study early. All three subjects experiencing the "flu-like". . .
DETD In clinical trial 004, specifically, the adverse reactions associated with weekly dosing of **rifalazil** are listed in Tables 8 and 9, and compared to 003 trial results. Tables 12 and 13 show the number and severity of drug-related adverse reactions associated with once-a-week administration of **rifalazil** vis-a-vis each subject and each dose in 004 clinical trial.
DETD As seen in Table 12, the number of adverse reactions observed following once-a-week administration of **rifalazil** to healthy volunteers was directly related to the dosage of **rifalazil** administered. When the dosage was 25 mg/week, there were forty-six adverse reactions. When the dosage was 50 mg/week, then there. . .
DETD Details of the adverse reactions associated with weekly dosing of **rifalazil** appear in Tables 8, 9, 12 and 13. All eighteen subjects completed the 004 clinical trial. Fewer unique adverse reactions. . .
DETD . . . measurement remained within the normal established ranges. In clinical trial 003, all subjects in Group 1 receiving 25 mg of **rifalazil**/day discontinued the study early.

DETD . . . plots of white blood cell (WBC) counts of healthy volunteers receiving dosages 0 mg, 5 mg and 25 mg of **rifalazil** administered daily. Normal range of white blood cell counts, shown in the FIG. 1 as "L" and "H" lines, is. . .

DETD FIG. 2 shows individual white blood cell counts in healthy volunteers (Group 1) receiving 25 mg of **rifalazil** daily for 14 days. As seen in FIG. 2, subjects in Group 1 experienced a larger drop in WBC counts,. . .

DETD FIG. 3 shows individual white blood cell counts in healthy volunteers (Group 2) receiving 5 mg of **rifalazil** daily for 14 days. As seen in FIG. 3, subjects in Group 2 experienced lower decreases in WBC counts which. . .

DETD . . . shows mean absolute neutrophil count in twenty-four healthy volunteers following administration of 0 mg, 5 mg and 25 mg of **rifalazil** daily for 14 days. As seen in FIG. 4, the absolute neutrophil count results have shown less consistent patterns making. .

DETD FIGS. 5 and 6 show individual absolute neutrophil counts in Group 1 receiving 25 mg of **rifalazil** daily for 14 days and Group 2 receiving 5 mg **rifalazil** daily for 14 days, respectively. Four subjects in Group 1, receiving 25 mg of **rifalazil**, seen in FIG. 5, and 3 subjects in Group 2, receiving 5 mg of **rifalazil** , seen in FIG. 6, experienced ANC values <2.0+10.sup.3 /mm.sup.3, however no ANC value fell below <1.0+10.sup.3 /mm.sup.3 for any individual. . .

DETD . . . in FIG. 7, demonstrated small changes relative to placebo, with fewer changes occurring in the group receiving 5 mg of **rifalazil** versus the group receiving 25 mg. All hematologic parameters returned to normal within 14 days following administration of the last. . .

DETD . . . mean white blood cell plots for once a week dosage of 0 mg (control), 25 mg and 50 mg of **rifalazil** for four weeks. The subjects' hematological parameters were followed for an additional two weeks up to day 36.

DETD When the results seen in FIG. 8 (once-a-week administration of 50 and 25 mg **rifalazil**) are compared to results seen in FIG. 1 (once-a-day administration of 5 and 25 mg of **rifalazil**), the differences in WBC counts are readily observed. In FIG. 1, both 50 and 25 dosages show continuous drop in. . .

DETD FIG. 9 shows mean absolute neutrophil counts for once-a-week dosage of 0 mg (control), 25 mg and 50 mg of **rifalazil** administered for four weeks. As above, subjects ANC were followed up to day 36. Three subjects in the 25 mg. . .

DETD FIG. 10 shows mean platelet plots for once-a-week dosage of 0 mg (control), 25 mg and 50 mg of **rifalazil** for four weeks with follow up to day 36. As seen in FIG. 10, once a week dosages of **rifalazil** on platelets were unremarkable without any observable changes outside of the normal range 150-450 K/CU MM.

DETD Pharmacokinetic analyses associated with clinical trials involved measurement of concentrations of **rifalazil** in plasma and/or whole blood of subjects participating in the four Phase 1 studies using high performance liquid chromatography. Most. . .

DETD . . . the 003 clinical trial and in Table 15 for the 004 clinical trial 004. Several pharmacokinetic patterns were consistently observed. **Rifalazil** appears to be slowly absorbed, widely distributed, and slowly eliminated via a multi-phasic process. Inter-patient variability was demonstrated.

DETD Due to extremely low levels of **rifalazil** measured in the urine, elimination of **rifalazil** seems to be non-renal, and probably occurs by the fecal route. In addition, low levels of oxidative metabolites of **rifalazil** were found in plasma. This further

suggests that drug is excreted in the feces either in unchanged form or as. . .

DETD . . . 22). Because of extensive sampling after the fourth dose, this study yielded the most complete data about terminal elimination of **rifalazil** given in a multiple-dose regimen. Results are shown in Table 15.

DETD . . . four Phase I clinical trials have investigated the safety profile and pharmacokinetics in healthy male subjects following the administration of **rifalazil** as single doses (300 mg, 100 mg, 30 mg), daily doses (25 mg, 5 mg) administered for 14 days, and. . .

DETD Pharmacokinetic analysis has clearly demonstrated that the administration of food with **rifalazil** delayed absorption and increased C.sub.max and AUC in a dose-proportional manner. The mean terminal half-life seen with the 25 mg dose was about 61 hours. Accumulation of **rifalazil** with either 25 mg or 50 mg doses, given once weekly over 4 weeks to healthy subjects, appeared to be. . .

DETD . . . which was 2 to 3 times the M1C.sub.90 of rifampin-sensitive Mycobacterium tuberculosis (15.6 ng/mL) Furthermore, because of the partitioning of **rifalazil** into macrophages, therapeutically beneficial concentrations of **rifalazil** are expected to persist in macrophages longer than in plasma. Thus, plasma concentrations that fall below the MIC.sub.90 during the. . .

DETD B. Efficacy of **Rifalazil** Treatment in TB Patients--Clinical Trial 005

DETD . . . or isoniazid combined with rifampin both administered daily, or isoniazid administered daily with either 10 mg or 25 mg of **rifalazil** administered weekly.

DETD . . . are shown in Table 18. WBC, ANC and platelet counts in patients treated with INH daily and 10/25 mg of **rifalazil** weekly, are shown in Tables 19 and 20, respectively. **Rifalazil** concentration in patients treated with INH and 10 or 25 mg of **rifalazil**, are shown in Table 21. Definite diagnosis and evaluation of treatment efficacy requires direct examination of sputum for the presence. . .

DETD . . . Group 2 received INH daily plus rifampin daily for 14 days, Group 3 received INH daily for 14 days plus **rifalazil** once per week (10 mg on day 1 and day 8) over 14 days, and Group 4 received INH daily for 14 days plus **rifalazil** once per week (25 mg on day 1 and day 8) over 14 days. Dosages of isoniazid and rifampin depended. . .

DETD . . . received daily treatment with INH in combination with rifampin administered daily (Group 2) or INH administered daily in combination with **rifalazil** administered once-a-week at 25 mg dosages (Group 4). These data show that **rifalazil** administered weekly or twice weekly in relatively very low dosages of 10 or 25 mg is an effective substitute for. . .

DETD . . . from Sputum Baseline to Day 15 in Log.sub.10 CFU/mL of Sputum Microbiologically Valuable Patients

	Treatment Group			
		INH + RMP	INH + **Rifalazil**	INH + **Rifalazil**
Log.sub.10 CFU/mL	INH 400 mg	400 mg + 600 mg	400 mg + 10 mg	400 mg + 25 mg
N	6	4. . .		

DETD These results clearly show that administration of INH-**rifalazil** once-a-week in 10 or particularly 25 mg doses is as efficacious treatment for tuberculosis as treatment with INH-rifampin daily.

DETD . . . in all groups during the treatment but did not reach critically low levels. Once a week treatment with 10 mg **rifalazil**

combined with 400 mg or less of INH administered daily did not lead to decrease in WBC.

DETD . . . drops below 1.0 K/CU MM. That level was reached in only one patient in Group 3, treated with INH plus **rifalazil** at 10 mg but that patient had a low ANC value to begin with.

DETD The important conclusions derived from the hematologic data is that **rifalazil** does not cause a greater level of hematologic disturbances (safety concerns) than rifampin which is routinely used for treatment of TB. **Rifalazil** is therefore as safe as rifampin and as efficacious in lower and less frequent dosages.

DETD TABLE 20

WBC, ANC, and Platelet Counts (K/CU MM)

INH + 25 mg-**Rifalazil**

	Baseline	Day 4	Day 8	Day 11	Day 15	Day 28	Day 42
WBC (K/cu mm)							
n	7	7	7	7	7	3	. . .

DETD Table 21 summarizes the plasma concentrations data of **rifalazil** measured in patients that received **rifalazil** at zero hour. The data are separated into 2 groups and are identified as INH+10 mg **rifalazil** (Group 3) and INH+25 mg **rifalazil** (Group 4). The concentration of **rifalazil** in plasma is presented in ng/mL and are shown as a timecourse (hours and days) wherein values were determined at. . .

DETD TABLE 21

Rifalazil Concentration in Plasma (ng/mL)

	Hour							Day 8	Day 8
Treatment Group	0	3	6	9	12	24	48	72	H-0	H-6. . .

DETD The observed plasma levels of **rifalazil** were similar to those seen in normal volunteers. Table 21 shows that the plasma concentration of **rifalazil** increases from the zero level to 9.7 ng/mL for 10 mg of **rifalazil** and to 15.93 ng/mL in three hours showing a maximum concentration of the drug in plasma at six hours following the drug administration (12.68 ng/mL for 10 mg **rifalazil** and 28.47 ng/mL for 25 mg **rifalazil**). The drug concentration in plasma slowly decreases but there is still measurable amount of drug in plasma at 72 hours. . .

DETD The data obtained in TB patients show that **rifalazil** administered once or twice weekly is effective for treatment of tuberculosis and has lesser adverse reactions than other currently available. . .

DETD C. Comparison of **Rifalazil** Treatment with Rifampin and Rifabutin

DETD GI reactions included **heartburn**, epigastric distress, anorexia, nausea, vomiting, gas, cramps, diarrhea, sore mouth and tongue, pseudomembranous colitis, pancreatitis, and were experienced by 1%. . .

DETD **Rifalazil** has been shown to have antibacterial activity against Mycobacterium tuberculosis, Mycobacterium avium, Chlamydia pneumoniae, H. pylori and other bacteria. Despite the adverse reactions described in the clinical trials 001-004, the novel method for treatment of tuberculosis with **rifalazil** administered once or twice-a-week is a method of choice. It effectively lowers CFU in TB patients when administered in well. . .

DETD Both the animal studies and studies on human volunteers suggest that **rifalazil** has fewer side effects than rifampin, and rifabutin

and has higher anti-bacterial activity, especially against Mycobacterium tuberculosis, Mycobacterium avium, Chlamydia. . .

DETD **Rifalazil** may be formulated and administered as standalone drug with various pharmaceutically acceptable additives and excipients, or in combination with other. . . the disease. Various combinations and ratios of drugs to each other are within the skills of the pharmacist formulating the **rifalazil** or **rifalazil** combination with other drugs.

DETD Typically, the drug product will contain **rifalazil**, mannitol, USP; hydroxypropyl cellulose, NF; colloidal silicon, dioxide, NF; magnesium stearate, NF; polysorbate 80, NF; and water in proportions that permit material flow in capsule-filling equipment. For example, **rifalazil** will be prepared in No. 3 hard gelatin dark blue opaque snap fit capsules, or as tablets, injectables, suppositories, etc.

DETD For clinical studies described above, **rifalazil** capsules have been prepared at several different strengths; 5 mg, 25 mg, 50 mg, and 100 mg. The drug in. . .

DETD Subjects in an open-label trial received a single or multiple dose of 5, 25, 50 or 300 mg dose of **rifalazil.** The study was a randomized, double-blind, placebo-controlled intermittent dose study designed to determine a maximum safe dosing regimen.

DETD . . . into two treatment groups, each consisting of six subjects. Subjects in each group were randomized to receive either placebo or **rifalazil** once weekly for 4 weeks with a two-week follow-up period. The two treatment groups were separated by at least two. . .

DETD Dose selection for this study was based on the safety profile of **rifalazil** obtained from three previous safety and pharmacokinetic (PK) studies. The results of these studies indicated that the incidence of adverse. . .

DETD **Rifalazil** and matching placebo were prepared in No.3 hard gelatin dark blue opaque snap-fit capsules. **Rifalazil** capsules have been prepared at four different strengths 5 mg, 25 mg, 50 mg and 100 mg. **Rifalazil** in the 5 mg, 25 mg and 50 mg strength capsules has been blended with additional mannitol (placebo) so that. . .

DETD . . . daily, which is also typical and FDA approved TB treatment, or with 400 mg isoniazid daily and 10 mg of **rifalazil** once-a-week, or with 400 isoniazid daily and 25 mg of **rifalazil** once-a-week. Both latest regimens were experimental and performed under IND permit from FDA.

CLM What is claimed is:

. . . by Mycobacterium tuberculosis, Mycobacterium avium complex, Chlamydia pneumoniae or Helicobacter pylori in human subjects by once-a-week or twice-a-week administration of **rifalazil** in a dosage from about 1 to about 100 mg.

2. The method of claim 1 wherein the dosage of **rifalazil** is from 5 to 50 mg administered once-a-week or twice-a-week.

3. The method of claim 2 wherein the dosage of **rifalazil** is from 10 to 25 mg administered once-a-week or twice-a-week.

6. The method of claim 5 wherein the tuberculosis is treated by once-a-week or twice-a-week administration of **rifalazil** for 4 to 62 weeks.

7. The method of claim 6 wherein **rifalazil** is administered in combination with isoniazid, ethambutol, pyrazinamide, streptomycin, capreomycin, ethionamide, cycloserine, kanamycin, tobramycin or

amikacin.

11. The method of claim 10 wherein the Chlamydia pneumoniae infection is treated with once-a-week or twice-a-week dose of **rifalazil** in dose from 1 to about 50 mg orally.

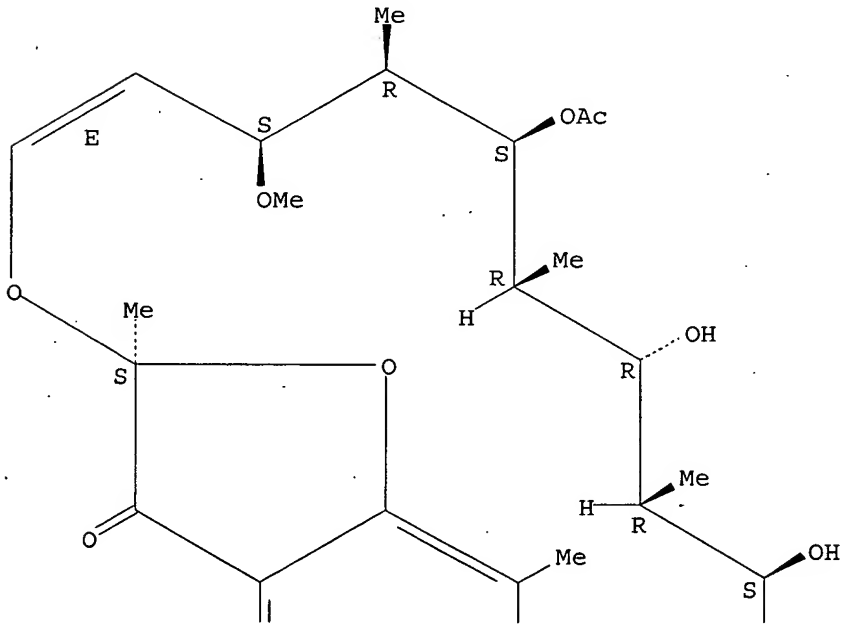
. . . of claim 12 wherein the Mycobacterium avium complex infection is treated with once-a-week or twice-a-week dose of 1-50 mg of **rifalazil** alone or in combination with azithromycin or clanthromycin.

14. The method of claim 1 wherein the **rifalazil** is administered orally, transdermally, parenterally, topically or by suppositories.

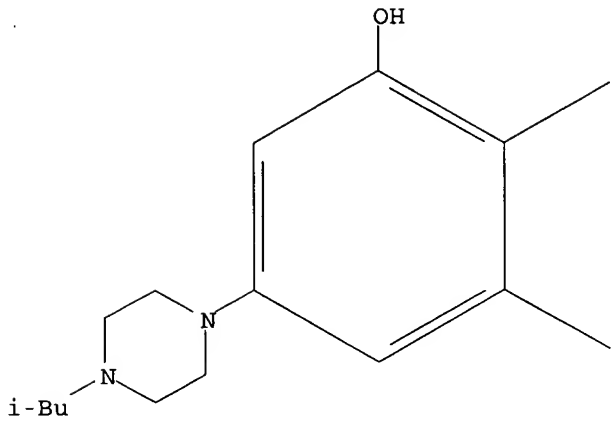
IT **129791-92-0**, Rifalazil
(rifalazil administered once- or twice-weekly for treatment of bacterial infection)
IT **129791-92-0**, Rifalazil
(rifalazil administered once- or twice-weekly for treatment of bacterial infection)
RN 129791-92-0 USPATFULL
CN Rifamycin VIII, 1',4-didehydro-1-deoxy-1,4-dihydro-3'-hydroxy-5'-[4-(2-methylpropyl)-1-piperazinyl]-1-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

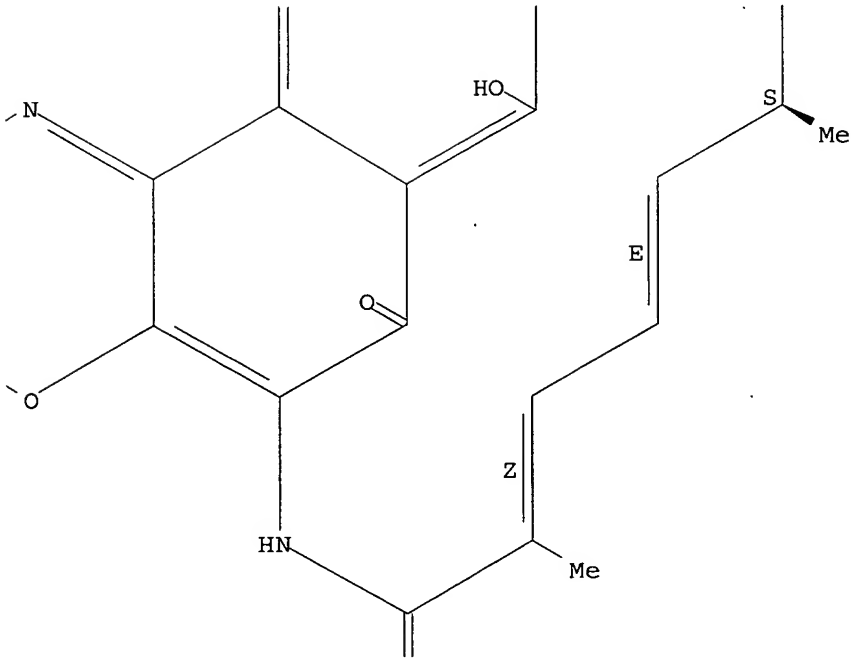
PAGE 1-B



PAGE 2-A



PAGE 2-B



PAGE 3-B

O

=>